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(54) NEW USE OF RFRP AND OT7T022

(57)Abstract:
PROBLEM TO BE SOLVED: To provide new uses of RFRP and OT7T022.
SOLUTION: The RFRP and OT7T022 (a receptor protein of RFRP), DNA encoding the substances and OT7T022 agonist are useful as an agent for the prevention/treatment/amelioration of adrenal insufficiency, spasm, aggressive behavior, gait abnormality, elevation of body temperature, decrease in white blood cell count, decrease in platelet count, increase in locomotor activity or loss of muscle strength. A non-human animal of O7T022 gene expression insufficiency is useful for the screening of the preventing/treating/ameliorating agent for the above diseases.

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CLAIMS

[Claim(s)]
[Claim 1]
Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.
[Claim 2]
a polypeptide -- array number: -- 1 and array number: -- ** according to claim 1 which is the polypeptide which consists of an amino acid sequence expressed with 3, array number:5, array number:7, array number:9, or array number:22.
[Claim 3]
A partial peptide
(i) -- array number: -- 1 or array number: -- the peptide which consists of the 56th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 3, the 70th - (Met) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(ii) -- array number: -- 1 or array number: -- the peptide which consists of the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3,
(iii) array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 101st - (Asn) 131st (Phe) The 104th - (Asn) 131st (Phe) and the 115th - (Asn) 131st (Phe) The peptide which consists of the 124th - (Val) 131st (Phe), the 125th - (Pro) 131st (Phe), the 126th - (Asn) 131st (Phe), or the 127th - (Leu) the 131st amino acid sequence (Phe),
(iv) -- array number: -- the peptide which consists of the 58th - (Ser) 92nd

(Phe) of the amino acid sequence expressed with 5, the 70th - (Lys) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(v) -- array number: -- the peptide which consists of the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5,
(vi) -- array number: -- the amino acid sequence expressed with 5 the 101st - (Ser) 131st (Phe) The 104th - (Ala) 131st (Phe) and the 115th - (Asn) 131st (Phe) The peptide which consists of the 124th - (Val) 131st (Phe), the 125th - (Pro) 131st (Phe), the 126th - (Asn) 131st (Phe), or the 127th - (Leu) the 131st amino acid sequence (Phe),
Array number: (vii) The peptide which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 9, the 72nd - (Val) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe),
Array number: (viii) The peptide which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 9, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(ix) -- array number: -- the peptide which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 7 or 22, the 72nd - (Asp) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe),
(x) -- array number: -- the peptide which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 7 or 22, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(xi) Peptide with which 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) consists of amino acid sequences which carried out deletion,
(xii) The above (i) Peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of - (x),
(xiii) The above (i) Peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x),
(xiv) the peptide which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xv) ** according to claim 1 which is the peptide which consists of an amino acid sequence which combined the deletion, addition, insertion, and the permutation of above-mentioned (xi) - (xiv).
[Claim 4]

Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.

[Claim 5]

DNA -- array number: -- 1 and array number: -- ** according to claim 4 which is DNA which carries out the code of the polypeptide which consists of an amino acid sequence expressed with 3, array number:5, array number:7, array number:9, or array number:22.

[Claim 6]

DNA

(i) -- array number: -- 1 or array number: -- the peptide which consists of the 56th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 3, the 70th - (Met) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),

(ii) -- array number: -- 1 or array number: -- the peptide which consists of the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3,

(iii) array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 101st - (Asn) 131st (Phe) The 104th - (Asn) 131st (Phe) and the 115th - (Asn) 131st (Phe) The peptide which consists of the 124th - (Val) 131st (Phe), the 125th - (Pro) 131st (Phe), the 126th - (Asn) 131st (Phe), or the 127th - (Leu) the 131st amino acid sequence (Phe),

(iv) -- array number: -- the peptide which consists of the 58th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 5, the 70th - (Lys) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),

(v) -- array number: -- the peptide which consists of the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5,

(vi) -- array number: -- the amino acid sequence expressed with 5 the 101st - (Ser) 131st (Phe) The 104th - (Ala) 131st (Phe) and the 115th - (Asn) 131st (Phe) The peptide which consists of the 124th - (Val) 131st (Phe), the 125th - (Pro) 131st (Phe), the 126th - (Asn) 131st (Phe), or the 127th - (Leu) the 131st amino acid sequence (Phe),

Array number: (vii) The peptide which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 9, the 72nd - (Val) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro)

the 94th amino acid sequence (Phe),
Array number: (viii) The peptide which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 9, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(ix) -- array number: -- the peptide which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 7 or 22, the 72nd - (Asp) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe),
(x) -- array number: -- the peptide which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 7 or 22, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(xi) Peptide with which 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) consists of amino acid sequences which carried out deletion,
(xii) The above (i) Peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of - (x),
(xiii) The above (i) Peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x),
(xiv) the peptide which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xv) Peptide which consists of an amino acid sequence which combined the deletion, addition, insertion, and the permutation of above-mentioned (xi) - (xiv),
** according to claim 4 which is DNA which carries out a code.
[Claim 7]
Array number: The diagnostic agent of the myonosus which comes to contain DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior, or muscular power change.
[Claim 8]
Array number: The myonosus which comes to contain the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or

prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 9]

Array number: The diagnostic agent of the myonosus which comes to contain the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior, and muscular power change.

[Claim 10]

Array number: The myonosus which comes to contain the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 11]

Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain the compound to which the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1 or substantially, or its partial peptide is made to increase, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, thrombocytopenia, and the amount of spontaneous behavior, or muscular power lowering.

[Claim 12]

Array number: The myonosus which comes to contain the compound which decreases the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 13]

Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait

abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.

[Claim 14]

OT7T022 -- array number: -- 11 or array number: -- ** according to claim 13 which is the receptor protein which consists of an amino acid sequence expressed with 24.

[Claim 15]

Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.

[Claim 16]

DNA -- array number: -- 11 or array number: -- ** according to claim 15 which is DNA which carries out the code of receptor protein OT7T022 which consist of an amino acid sequence expressed with 24, or the partial peptide of those.

[Claim 17]

Array number: The diagnostic agent of the myonosus which comes to contain DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior, or muscular power change.

[Claim 18]

Array number: The myonosus which comes to contain the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 19]

Array number: The diagnostic agent of the myonosus which comes to contain the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, a

convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior, or muscular power change.

[Claim 20]

Array number: The myonosus which comes to contain the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 21]

Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain the agonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.

[Claim 22]

Array number: The myonosus which comes to contain the antagonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 23]

Array number: Prevention and therapy / improvement agent of the increment in the myonosus which comes to contain the compound to which the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11 or substantially, or the partial peptide of those is made to increase, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.

[Claim 24]

Array number: The myonosus which comes to contain the compound which decreases the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid

sequence expressed with 11, or substantially, or the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior.

[Claim 25]

As opposed to mammalian,

(i) -- array number: -- the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,

(ii) -- array number: -- DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,

Array number: (iii) The compound to which the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1 or substantially, or its partial peptide is made to increase, or its salt,

(iv) -- array number: -- receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,

(v) -- array number: -- DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,

(vi) -- array number: -- the agonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or

Array number: (vii) The increment in the myonosus characterized by prescribing for the patient the effective dose of the compound to which the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11 or substantially, or the partial peptide of those is made to increase, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or the prevention and therapy / improvement approach of muscular power lowering.

[Claim 26]

As opposed to mammalian,

(i) -- array number: -- the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,

(ii) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,
Array number: (iii) The compound which decreases the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, or its salt,
(iv) -- array number: -- the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,
(v) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,
(vi) -- array number: -- the antagonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number: (vii) The myonosus characterized by prescribing for the patient the effective dose of the compound which decreases the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the prevention and therapy / improvement approach of reduction of the amount of spontaneous behavior.
[Claim 27]
In order to manufacture prevention and therapy / improvement agent of the increment in the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering
(i) -- array number: -- the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,
(ii) -- array number: -- the compound to which the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed

with 1 or substantially, or its partial peptide, and the amino acid sequence expressed with array (iii) number:1, or substantially, or its partial peptide is made to increase, or its salt,
(iv) -- array number: -- receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,
(v) -- array number: -- DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,
(vi) -- array number: -- the agonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number: (vii) The activity of the compound to which the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11 or substantially, or the partial peptide of those is made to increase, or its salt.
[Claim 28]
In order to manufacture prevention and therapy / improvement agent of reduction of the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior
(i) -- array number: -- the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,
(ii) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,
Array number: (iii) The compound which decreases the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, or its salt,
(iv) -- array number: -- the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,
(v) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial

peptide of those,
(vi) -- array number: -- the antagonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number: (vii) The activity of the compound which decreases the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, or its salt.
[Claim 29]
The mammalian embryonic stem cell by which OT7T022 gene was inactivated.
[Claim 30]
The embryonic stem cell according to claim 29 which is drug tolerance.
[Claim 31]
The embryonic stem cell according to claim 29 whose drugs are neomycins.
[Claim 32]
The embryonic stem cell according to claim 29 in which OT7T022 gene was inactivated by insertion of a reporter gene.
[Claim 33]
The embryonic stem cell according to claim 32 whose reporter gene is a lacZ gene.
[Claim 34]
The embryonic stem cell according to claim 29 whose mammalian is a mouse.

[Claim 35]
OT7T022 gene -- array number: -- the embryonic stem cell according to claim 29 which is a gene containing the base sequence expressed with 12, array number:25, array number:26, array number:28, or array number:32.
[Claim 36]
OT7T 022 gene-expression insufficient nonhuman mammal.
[Claim 37]
The animal according to claim 36 for which OT7T022 gene was inactivated by insertion of a reporter gene.
[Claim 38]
The animal according to claim 36 whose nonhuman mammal is a mouse.
[Claim 39]
OT7T022 gene -- array number: -- the animal according to claim 36 which is a gene containing the base sequence expressed with 12, array number:28, or array number:32.
[Claim 40]
The animal according to claim 36 as which thymus involution delay is

regarded compared with a wild type nonhuman mammal.
[Claim 41]
The animal according to claim 36 as which the opisthoporeia is regarded compared with a wild type nonhuman mammal.
[Claim 42]
The animal according to claim 36 as which the torpor is regarded to a noxious stimulus compared with a wild type nonhuman mammal.
[Claim 43]
It compares with a wild type nonhuman mammal, and is an animal according to claim 36 with much offensive action.
[Claim 44]
The animal according to claim 36 as which lowering of kidney absolute weight or thymus gland absolute weight is regarded compared with a wild type nonhuman mammal.
[Claim 45]
The animal according to claim 36 as which reduction of a white blood cell count or a platelet count is regarded compared with a wild type nonhuman mammal.
[Claim 46]
The animal according to claim 36 to which muscular power is falling compared with a wild type nonhuman mammal.
[Claim 47]
It is characterized by using the cell originating in an animal according to claim 36, its organization, or them. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or the screening approach of prevention and therapy / improvement medicine muscular power lowering.
[Claim 48]
The screening approach according to claim 47 characterized by medicating the cell originating in an animal according to claim 36, its organization, or them with a trial compound.
[Claim 49]
The symptoms model animal produced by mating with an animal according to claim 36 and other symptoms model animals.
[Claim 50]
The symptoms model animal produced with the drugs induction or the stress load to an animal according to claim 36.

[Claim 51]
The **** model animal produced with the drugs induction or the stress load to an animal according to claim 49.
[Claim 52]
It is characterized by using the cell originating in an animal according to claim 49 to 51, its organization, or them. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or the screening approach of prevention and therapy / improvement medicine muscular power lowering.
[Claim 53]
It is characterized by medicating the cell originating in an animal according to claim 49 to 51, its organization, or them with a trial compound. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or the screening approach of prevention and therapy / improvement medicine muscular power lowering.
[Claim 54]
The compound which promotes or checks the promotor activity over OT7T022 gene characterized by medicating an animal according to claim 37 with a trial compound, and detecting the manifestation of a reporter gene, or the screening approach of the salt.
[Claim 55]
Array number : The polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, The partial peptide, its amide, its ester, or its salt, and (or) array number: -- the myonosus characterized by using receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- The increment in adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the screening approach

of prevention and therapy / improvement medicine reduction of the amount of spontaneous behavior.

[Claim 56]

Array number : The polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, The partial peptide, its amide, its ester, or its salt, and (or) array number: -- the myonosus which comes to contain receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- The increment in adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the kit for screening of prevention and therapy / improvement medicine of reduction of the amount of spontaneous behavior.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to the new application of OT7T022 which are the receptor protein of RFRP and RFRP.
Furthermore, this invention relates to prevention and therapy / improvement medicine in which it obtains and deals by the embryonic stem cell of the nonhuman mammal by which OT7T022 gene was inactivated, the OT7T 022 gene-expression insufficient nonhuman mammal, the screening approach using them, and its screening.
[0002]
[Description of the Prior Art]
The peptide (RFRP-1, RFRP-2, RFRP-3) of Mr. LPL RF amide, Mr. LPL RS amide, Mr. LPQ RF amide, or Mr. LPL RLamide is reported for the C terminal combined with new acceptor OT7T022 and new it (patent reference 1).
It is reported that OT7T022, RFRP-1 and RFRP-2, and RFRP-3 are participating in prolactin secretion (patent reference 2).
It is indicated that NPSF corresponding to RFRP-1 and NPVF corresponding to RFRP-3 combine with OT7T022, and are participating in anti-opioid (nonpatent literature 1).
However, many points which should be solved further are left behind about the function and action mechanism of OT7T022 RFRP and in the living body.
[0003]
[Patent reference 1]
WO 00/No. 29441
[Patent reference 2]
WO 01/No. 66134
[Nonpatent literature 1]
The Journal of Biological Chemistry, vol.276, No.40, p36961-36969, 2001
[0004]
[Problem(s) to be Solved by the Invention]
If it succeeds in production of the nonhuman animal embryonic stem cell by which OT7T022 gene was inactivated, an OT7T 022 gene-expression insufficient nonhuman animal can be created. And since the OT7T 022 gene-expression insufficient nonhuman animal obtained carries out deletion of the various bioactive which may be

guided by OT7T022, it serves as a model of the disease which considers inactivation of the bioactive of OT7T022 as a cause, and cause investigation of these diseases and the examination of a cure of it are attained.
This invention solves RFRP and the further function of OT7T022, and makes it a technical problem to offer a new remedy.
[0005]
[Means for Solving the Problem]
this invention persons succeed in creating an OT7T 022 gene-expression insufficient nonhuman animal, as a result of repeating research wholeheartedly in view of the above-mentioned technical problem. As a manifestation mold of this animal It found out that lowering of reduction of the feverscence, kidney absolute weight increase, thymus gland absolute weight increase, and a white blood cell count, reduction of a platelet count, the increment in the amount of spontaneous behavior (especially night the amount of spontaneous behavior), induction of aggressive behavior, the opisthoporeia, and muscular power etc. took place also unexpectedly. this invention persons came to complete this invention, as a result of repeating examination further based on these knowledge.
[0006]
Namely, this invention,
[1] Array number : the increment in the myonosus which comes to contain the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,

[2] a polypeptide -- array number: -- 1, array number:3, array number:5, array number:7, array number:9, or ** given in array number:above-mentioned [which is the polypeptide which consists of an amino acid sequence expressed with 22] [1],
[3] A partial peptide
The 88th - (Leu) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with 3 is contained. (i) -- array number: -- 1 or array number: -- To the amino terminal side of the amino acid sequence respectively -- array number: -- the peptide (Homo sapiens RFRP-1) which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 87th amino acid sequence (Asn) of the amino acid sequence expressed with 1 or 3, and 1-87 amino acid may add,
The 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3 is contained. (ii) -- array number: -- 1 or array number: -- To the amino terminal side of the amino acid sequence respectively -- array number: -- the peptide (Homo sapiens RFRP-2) which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 100th amino acid sequence (Arg) of the amino acid sequence expressed with 1 or 3, and 1-100 amino acid may add,
The 127th - (Leu) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 3 is contained. (iii) array number: -- 1 or array number: -- To the

amino terminal side of the amino acid sequence respectively -- array number: -- the peptide (Homo sapiens RFRP-3) which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 126th amino acid sequence (Asn) of the amino acid sequence expressed with 1 or 3, and 1-126 amino acid may add,
(iv) -- array number: -- the peptide (cow RFRP-1) which consists of an amino acid sequence which could contain the 88th - (Leu) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with 5, could count from the C terminal of the 1st - (Met) the 87th amino acid sequence (Lys) of the amino acid sequence expressed with array number:5 to the amino terminal side of the amino acid sequence, and 1-87 amino acid may add,
(v) -- array number: -- the peptide (cow RFRP-2) which consists of an amino acid sequence which could contain the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5, could count from the C terminal of the 1st - (Met) the 100th amino acid sequence (Arg) of the amino acid sequence expressed with array number:5 to the amino terminal side of the amino acid sequence, and 1-100 amino acid may add,
(vi) -- array number: -- the peptide (cow RFRP-3) which consists of an amino acid sequence which could contain the 127th - (Leu) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 5, could count from the C terminal of the 1st - (Met) the 126th amino acid sequence (Asn) of the amino acid sequence expressed with array number:5 to the amino terminal side of the amino acid sequence, and 1-126 amino acid may add,
Array number: (vii) The peptide which consists of an amino acid sequence which could contain the 90th - (Leu) the 94th amino acid sequence (Phe) of the amino acid sequence expressed with 9, could count from the C terminal of the 1st - (Met) the 89th amino acid sequence (Asn) of the amino acid sequence expressed with array number:9 to the amino terminal side of the amino acid sequence, and 1-89 amino acid may add (mouse RFRP-1),
Array number: (viii) The peptide which consists of an amino acid sequence which could contain the 121st - (Leu) the 125th amino acid sequence (Phe) of the amino acid sequence expressed with 9, could count from the C terminal of the 1st - (Met) the 120th amino acid sequence (Ser) of the amino acid sequence expressed with array number:9 to the amino terminal side of the amino acid sequence, and 1-120 amino acid may add (mouse RFRP-3),
(ix) -- array number: -- the 90th - (Leu) the 94th amino acid sequence (Phe) of the amino acid sequence expressed with 7 or 22 -- containing -- the amino terminal side of the amino acid sequence -- respectively -- array number: -- the peptide (Latt RFRP-1) which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 89th amino acid sequence (Val) of the amino acid sequence expressed with 7 or 22, and 1-89 amino acid may add,
(x) -- array number: -- the 121st - (Leu) the 125th amino acid sequence (Phe) of the amino acid sequence expressed with 7 or 22 -- containing -- the amino terminal side of the amino acid sequence -- respectively -- array number: -- the peptide (Latt RFRP-3) which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 120th amino acid sequence (Ser) of the amino acid sequence expressed with 7 or 22, and 1-120 amino acid may add,

(xi) Peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of above-mentioned (i) - (x),
(xii) The above (i) Peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x),
(xiii) the peptide which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xiv) ** of the above-mentioned [1] publication which is the peptide which consists of an amino acid sequence which combined addition, insertion, and the permutation of above-mentioned (xi) - (xiii),
[4] A partial peptide
(i) -- array number: -- 1 or array number: -- the peptide (Homo sapiens RFRP-1) which consists of the 56th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 3, the 70th - (Met) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(ii) -- array number: -- 1 or array number: -- the peptide (Homo sapiens RFRP-2) which consists of the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3,
(iii) array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 101st - (Asn) 131st (Phe) The 104th - (Asn) 131st (Phe) and the 115th - (Asn) 131st (Phe) The 124th - (Val) 131st (Phe) and the 125th - (Pro) 131st (Phe) The peptide which consists of the 126th - (Asn) 131st (Phe) or the 127th - (Leu) the 131st amino acid sequence (Phe) (Homo sapiens RFRP-3),
(iv) -- array number: -- the peptide (cow RFRP-1) which consists of the 58th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 5, the 70th - (Lys) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(v) -- array number: -- the peptide (cow RFRP-2) which consists of the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5,
(vi) -- array number: -- the amino acid sequence expressed with 5 the 101st - (Ser) 131st (Phe) The 104th - (Ala) 131st (Phe) and the 115th - (Asn) 131st (Phe) The 124th - (Val) 131st (Phe) and the 125th - (Pro) 131st (Phe) The peptide which consists of the 126th - (Asn) 131st (Phe) or the 127th - (Leu) the 131st amino acid sequence (Phe) (cow RFRP-3),
Array number: (vii) The peptide which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 9, the 72nd - (Val) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe) (mouse RFRP-1),
Array number: (viii) The peptide which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 9, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe) (mouse RFRP-3),
(ix) -- array number: -- the peptide (Latt RFRP-1) which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 7 or 22, the 72nd - (Asp) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe)
(x) -- array number: -- the peptide (Latt RFRP-3) which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 7 or 22, the 119th -

(Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(xi) Peptide with which 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) consists of amino acid sequences which carried out deletion (deletion mold),
(xii) The above (i) Peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of - (x) (addition mold),
(xiii) The above (i) Peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x) (inserting type),
(xiv) the peptide (permutation mold) which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xv) ** of the above-mentioned [1] publication which is the peptide which consists of an amino acid sequence which combined the deletion, addition, insertion, and the permutation of above-mentioned (xi) - (xiv),
[5] Array number : the increment in the myonosus which comes to contain DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,
[6] DNA -- array number: -- the 1, array number:3, array number:5, array number:7, array number:9, or array number:above-mentioned [5] publication which is DNA which carries out the code of the polypeptide which consists of an amino acid sequence expressed with 22 -- **
[7] DNA
(i) -- array number: -- 1 or array number: -- the peptide (Homo sapiens RFRP-1) which consists of the 56th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 3, the 70th - (Met) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(ii) -- array number: -- 1 or array number: -- the peptide (Homo sapiens RFRP-2) which consists of the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3,
(iii) array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 101st - (Asn) 131st (Phe) The 104th - (Asn) 131st (Phe) and the 115th - (Asn) 131st (Phe) The 124th - (Val) 131st (Phe) and the 125th - (Pro) 131st (Phe) The peptide which consists of the 126th - (Asn) 131st (Phe) or the 127th - (Leu) the 131st amino acid sequence (Phe) (Homo sapiens RFRP-3),
(iv) -- array number: -- the peptide (cow RFRP-1) which consists of the 58th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 5, the 70th - (Lys) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(v) -- array number: -- the peptide (cow RFRP-2) which consists of the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5,
(vi) -- array number: -- the amino acid sequence expressed with 5 the 101st - (Ser)

131st (Phe) The 104th - (Ala) 131st (Phe) and the 115th - (Asn) 131st (Phe) The 124th - (Val) 131st (Phe) and the 125th - (Pro) 131st (Phe) The peptide which consists of the 126th - (Asn) 131st (Phe) or the 127th - (Leu) the 131st amino acid sequence (Phe) (cow RFRP-3),
Array number: (vii) The peptide which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 9, the 72nd - (Val) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe) (mouse RFRP-1),
Array number: (viii) The peptide which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 9, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe) (mouse RFRP-3),
(ix) -- array number: -- the peptide (Latt RFRP-1) which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 7 or 22, the 72nd - (Asp) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe)
(x) -- array number: -- the peptide (Latt RFRP-3) which consists of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 7 or 22, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(xi) Peptide with which 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) consists of amino acid sequences which carried out deletion (deletion mold),
(xii) The above (i) Peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of - (x) (addition mold),
(xiii) The above (i) Peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x) (inserting type),
(xiv) the peptide (permutation mold) which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xv) Peptide which consists of an amino acid sequence which combined the deletion, addition, insertion, and the permutation of above-mentioned (xi) - (xiv),
** of the above-mentioned [5] publication which is DNA which carries out a code,
[8] Array number : the diagnostic agent of the myonosus which comes to contain DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power change,
[9] Array number : the myonosus which comes to contain the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially

night the amount of spontaneous behavior),
[10] Array number : the diagnostic agent of the myonosus which comes to contain the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), and muscular power change,
[11] Array number : the myonosus which comes to contain the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),
[12] An array number : the increment in the myonosus which comes to contain the compound to which the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1 or substantially, or its partial peptide is made to increase, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white-blood-cell-count reduction, thrombocytopenia, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or the prevention and therapy / improvement agent of muscular-power lowering,
[13] Array number : the myonosus which comes to contain the compound which decreases the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),
[14] Array number : the increment in the myonosus which comes to contain receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,
[15] OT7T022 -- array number: -- ** of the above-mentioned [14] publication which is the receptor protein which consists of an amino acid sequence expressed with 11,
[16] Array number : the increment in the myonosus which comes to contain DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement

agent of muscular power lowering,
[17] DNA -- array number: -- the receptor protein OT7T above-mentioned [16] publication it is unstated from the amino acid sequence expressed with 11 and which is DNA which carries out the code of 022 or the partial peptide of those -- **
[18] Array number : the diagnostic agent of the myonosus which comes to contain DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power change,
[19] Array number : the myonosus which comes to contain the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),
[20] Array number : the diagnostic agent of the myonosus which comes to contain the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power change,
[21] Array number : the myonosus which comes to contain the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),
[22] Array number : the increment in the myonosus which comes to contain the agonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,
[23] Array number : the myonosus which comes to contain the antagonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially night the

amount of spontaneous behavior),
[24] An array number : the increment in the myonosus which comes to contain the compound to which the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11 or substantially, or the partial peptide of those is made to increase, or its salt, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white-blood-cell-count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or the prevention and therapy / improvement agent of muscular-power lowering,
[25] Array number : the myonosus which comes to contain the compound which decreases the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),
[26] As opposed to mammalian,
(i) -- array number: -- the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,
(ii) -- array number: -- DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,
Array number: (iii) The compound to which the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1 or substantially, or its partial peptide is made to increase, or its salt,
(iv) -- array number: -- receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,
(v) -- array number: -- DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,
(vi) -- array number: -- the agonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number : Myonosus, adrenal insufficiency which are characterized by prescribing for the patient the effective dose of the compound to which the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11 or substantially, or the partial peptide of those is made to increase, or its salt, (vii) The increment in a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or the prevention and therapy / improvement approach of muscular power lowering,

[27] As opposed to mammalian,
(i) -- array number: -- the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,
(ii) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,
Array number: (iii) The compound which decreases the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, or its salt,
(iv) -- array number: -- the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,
(v) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,
(vi) -- array number: -- the antagonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number: (vii) The myonosus characterized by prescribing for the patient the effective dose of the compound which decreases the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the prevention and therapy / improvement approach of reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),
[28] In order to manufacture prevention and therapy / improvement agent of the increment in the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power lowering
(i) -- array number: -- the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,
(ii) -- array number: -- DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,
Array number: (iii) The compound to which the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1 or substantially, or its partial peptide is made to increase, or its salt,
(iv) -- array number: -- receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,

(v) -- array number: -- DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,
(vi) -- array number: -- the agonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number: (vii) The compound to which the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11 or substantially, or the partial peptide of those is made to increase, or the activity of the salt,
[29] In order to manufacture prevention and therapy / improvement agent of reduction of the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially night the amount of spontaneous behavior)
(i) -- array number: -- the antibody to the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, its partial peptide, its amide, its ester, or its salt,
(ii) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide,
Array number: (iii) The compound which decreases the amount of manifestations of the polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, or its partial peptide, or its salt,
(iv) -- array number: -- the antibody to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt,
(v) -- array number: -- the antisense DNA which contains a complementary base sequence or its part in DNA which carries out the code of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those,
(vi) -- array number: -- the antagonist to receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- or
Array number: (vii) The compound which decreases the amount of manifestations of receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or the partial peptide of those, or the activity of the salt,
[30] The mammalian embryonic stem cell by which OT7T022 gene was inactivated,
[31] The embryonic stem cell of the above-mentioned [30] publication which is drug tolerance,
[32] The embryonic stem cell of the above-mentioned [29] publication whose drugs are neomycins,
[33] The embryonic stem cell of the above-mentioned [30] publication by which OT7T022 gene was inactivated by insertion of a reporter gene,
[34] The embryonic stem cell of the above-mentioned [33] publication whose reporter gene is a lacZ gene,

[35] The embryonic stem cell of the above-mentioned [30] publication whose mammalian is a mouse,
[36] OT7T022 gene -- array number: -- 12, array number:25, array number:26, array number:28, or an embryonic stem cell given in array number:above-mentioned [which is a gene containing the base sequence expressed with 32] [30],
[37] OT7T 022 gene-expression insufficient nonhuman mammal,
[38] The animal of the above-mentioned [37] publication by which OT7T022 gene was inactivated by insertion of a reporter gene,
[39] The animal of the above-mentioned [37] publication whose nonhuman mammal is a mouse,
[40] OT7T022 gene -- array number: -- 12, array number:28, or an animal given in array number:above-mentioned [which is a gene containing the base sequence expressed with 32] [37],
[41] The animal of the above-mentioned [37] publication as which thymus involution delay is regarded compared with a wild type nonhuman mammal,
[42] The animal of the above-mentioned [37] publication as which the opisthoporeia is regarded compared with a wild type nonhuman mammal,
[43] The animal of the above-mentioned [37] publication as which the torpor is regarded to a noxious stimulus (an example, heat noxious stimulus) compared with a wild type nonhuman mammal,
[44] Compare with a wild type nonhuman mammal and it is the animal of the above-mentioned [37] publication with much offensive action,
[45] The animal of the above-mentioned [37] publication as which lowering of kidney absolute weight or thymus gland absolute weight is regarded compared with a wild type nonhuman mammal,
[46] The animal of the above-mentioned [37] publication as which reduction of a white blood cell count or a platelet count is regarded compared with a wild type nonhuman mammal,
[47] The animal of the above-mentioned [37] publication to which muscular power is falling compared with a wild type nonhuman mammal,
[48] It is characterized by using the cell originating in the animal of the above-mentioned [37] publication, its organization, or them. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or the screening approach of prevention and therapy / improvement medicine muscular power lowering,
[49] The screening approach of the above-mentioned [48] publication characterized by medicating the cell originating in the animal of the above-mentioned [37] publication, its organization, or them with a trial compound,
[50] The increment in a nociception failure [which be acquired by the screening approach of the above-mentioned [48] publication], eye disease, hypophysis disease, myonosus, heart disease, hemopathy, kidney disease, immunopathy, adrenal insufficiency, eating disorder, obesity, emotional-disorder, schizophrenia, depression,

uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white-blood-cell-count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement medicine of muscular-power lowering,
[51] The nociception failure which comes to contain prevention and therapy / improvement medicine obtained by the screening approach of the above-mentioned [48] publication, An eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, The increment in an adrenal insufficiency, eating disorder, obesity, emotional-disorder, schizophrenia, depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,

[52] The symptoms model animal produced by mating with the animal of the above-mentioned [37] publication, and other symptoms model animals,
[53] The symptoms model animal produced with the drugs induction or the stress load to the animal of the above-mentioned [37] publication,
[54] The **** model animal produced with the drugs induction or the stress load to the animal of the above-mentioned [52] publication,
[55] It is characterized by using the cell originating in the animal of a publication, its organization, or them for either of above-mentioned [52]- [54]. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or the screening approach of prevention and therapy / improvement medicine muscular power lowering,
[56] It is characterized by prescribing a trial compound for the patient at the cell originating in an animal given in either of above-mentioned [52]- [54], its organization, or them. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or the screening approach of prevention and therapy / improvement medicine muscular power lowering,
[57] Are obtained by the screening approach the above [55] or given in [56]. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, The increment in a depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a

decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement medicine of muscular power lowering,
[58] The nociception failure which comes to contain prevention and therapy / improvement medicine obtained by the screening approach the above [55] or given in [56], An eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, The increment in an adrenal insufficiency, eating disorder, obesity, emotional-disorder, schizophrenia, depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,

[59] The compound which promotes or checks the promotor activity over OT7T022 gene characterized by medicating the animal of the above-mentioned [38] publication with a trial compound, and detecting the manifestation of a reporter gene, or the screening approach of the salt,
[60] The compound which promotes or checks the promotor activity over OT7T022 gene in which it obtains and deals by the screening approach of the above-mentioned [59] publication, or its salt,
[61] The nociception failure which comes to contain the compound which promotes the promotor activity over OT7T022 gene in which it obtains and deals by the screening approach of the above-mentioned [59] publication, or its salt, An eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, The increment in an adrenal insufficiency, eating disorder, obesity, emotional-disorder, schizophrenia, depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or prevention and therapy / improvement agent of muscular power lowering,

[62] The myonosus which comes to contain the compound which checks the promotor activity over OT7T022 gene in which it obtains and deals by the screening approach of the above-mentioned [59] publication, or its salt, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count or the prevention and therapy / improvement agent of reduction of the amount (especially night the amount of spontaneous behavior) of spontaneous behavior, a painkiller, the analgesic action accelerator of morphine, a morphine resistance evasion agent, or a morphine dependency evasion agent,
Array number : [63] The polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, The partial peptide, its amide, its ester, or its salt, and (or) array number: -- the myonosus characterized by using receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- Adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, the increment in a decrease of platelets and the amount of spontaneous

behavior (especially night the amount of spontaneous behavior), muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the screening approach of prevention and therapy / improvement medicine reduction reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior) -- and
Array number : [64] The polypeptide which contains the same amino acid sequence identically to the amino acid sequence expressed with 1, or substantially, The partial peptide, its amide, its ester, or its salt, and (or) array number: -- the myonosus which comes to contain receptor protein OT7T022 which contain the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, the partial peptide of those, or its salt -- Adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, The kit for screening of prevention and therapy / improvement medicine of reduction of the increment in a decrease of platelets and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially night the amount of spontaneous behavior) is offered.
[0007]
[Embodiment of the Invention]
The polypeptide which contains the same amino acid sequence identically [RFRP used by this invention] to the amino acid sequence expressed with array number:1, or substantially It is (calling RFRP hereafter). Homo sapiens and a homeotherm for example, a guinea pig, Latt, a mouse, a fowl, a rabbit, and Buta -- cells (for example, a retinal cell, hepatocyte, and splenic cells --), such as a sheep, a cow, and an ape A nerve cell, a neuroglia, a pancreas beta cell, a bone marrow cell, a mesangial cell, Langerhans cell, an epidermal cell, an epithelial cell, an endothelial cell, fibrocyte, a desmacyte, a muscle cell, a fat cell, and immunocyte (an example, a macrophage, and a T cell --) A B cell, a spontaneous killer cell, a mast cell, neutrophil leucocyte, basophilic leucocyte, eosinophile leucocyte, Monocyte, megakaryocyte, a synovial cell, chondrocyte, osteocyte, osteoblast, an osteoclast, An alveolar epithelial cell, hepatocyte, an interstitial cell, or the precursor cell of these cells, All the organizations where those cells, such as a stem cell or a cancer cell, exist, about (an example, a retina, an olfactory bulb, an amygdaloid nucleus, and a cerebrum -- the base -- a ball and a hippocampus --) each part of a brain and a brain A thalamus, hypothalamus, the cerebral cortex, a medulla oblongata, a cerebellum, a spine, a hypophysis, the stomach, the pancreas, The kidney, liver, a gonad, the thyroid, the gallbladder, bone marrow, a suprarenal gland, the skin, muscles, lungs, An alimentary canal (an example, the large intestine, small intestine), a blood vessel, the heart, a thymus gland, a spleen, an submaxillary gland, peripheral blood, The cell or its cultured cells of a corpuscle system, such as a prostate gland, a testis, the ovary, a placenta, a uterus, a bone, a joint, and skeletal muscle (For example) MEL, M1, CTLL-2, HT-2, WEHI-3, HL-60, JOSK-1, K562, ML-1, MOLT-3, MOLT-4, MOLT-10, CCRF-CEM, TALL-1, Jurkat, CCRT-HSB -2, KE-37, SKW-3, You may be a polypeptide originating in HUT-78, HUT-102, H9 and U937, THP-1, HEL, JK-1, CMK,--812, MEG-01, etc., and may be synthetic polypeptide.
Array number: The amino acid sequence which has about 95% or more of homology

still more preferably is raised about 90% or more more preferably about 80% or more as as substantially as the amino acid sequence expressed with 1 preferably about 70% or more as the amino acid sequence expressed with array number:1 as the same amino acid sequence.
The homology of an amino acid sequence can calculate on condition that the following (expected-value = 10;; which allows a gap matrix = BLOSUM62; filtering = OFF) using homology computational algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool). For example, array number:3, array number:5, array number:7, array number:9 or an array number the amino acid sequence expressed with array number:1, the amino acid sequence which has substantially the 22-180th amino acid sequences of the amino acid sequence expressed with array number:1 as the same amino acid sequence, and: The amino acid sequence expressed with 22 is raised.
[0008]
RFRP used for this invention specifically With the amino acid sequence expressed with the polypeptide which consists of an amino acid sequence expressed with 1, or array number:1, substantially The aforementioned array number : The same amino acid sequence (For example, it has the amino acid sequence expressed with array number:3, array number:5, array number:7, array number:9, or array number:22.) Array number: They are the polypeptide which consists of an amino acid sequence expressed with 1, and the polypeptide which has homogeneous prolactin secretion acceleration activity etc. substantially.
It is substantially indicated to be the same quality that prolactin secretion acceleration activity etc. is homogeneous in property (example, in biochemistry or in pharmacology). Therefore, although it is desirable that prolactin secretion acceleration activity is an EQC (an example, about 0.1 to 100 times, preferably about 0.5 to 10 times, more preferably 0.5 to 2 twice), quantitative elements, such as extent of such activity and molecular weight of a polypeptide, may differ.
measurement of prolactin secretion acceleration activity -- the very thing -- although it can carry out according to a well-known approach, according to the example 1 of WO 01/No. 66134, it can measure, for example.
As RFRP, for example Moreover, **1 The amino acid sequence, **2 in which 1-20 amino acid (preferably 1-15 pieces, still more preferably 1-5 pieces, more preferably 1-3 pieces) in the amino acid sequence expressed with 1, array number:3, array number:5, array number:7, array number:9, or array number:22 carried out deletion Array number : The amino acid sequence, **3 which 1-20 amino acid (preferably 1-15 pieces, still more preferably 1-5 pieces, more preferably 1-3 pieces) added to the amino acid sequence expressed with 1, array number:3, array number:5, array number:7, array number:9, or array number:22 Array number : The amino acid sequence, **4 by which 1-20 amino acid (preferably 1-15 pieces, still more preferably 1-5 pieces, more preferably 1-3 pieces) was inserted in the amino acid sequence expressed with 1, array number:3, array number:5, array number:7, array number:9, or array number:22 Array number : Array number : The amino acid sequence by which 1-20 amino acid (preferably 1-15 pieces, still more preferably 1-5 pieces, more preferably 1-3 pieces) in the amino acid sequence expressed with 1, array number:3, array number:5, array number:7, array number:9, or array number:22 was permuted from other amino acid, or **5 The polypeptide which has the amino acid sequence

which combined these deletion, addition, insertion, and a permutation is also contained.
As mentioned above, especially as for the location of the deletion, addition, insertion, or a permutation, an amino acid sequence is not limited, when adding, inserting or permuting, deletion and.
[0009]
According to the practice of a peptide mark, a left end is an amino terminal (amino terminus), and the right end of the polypeptide in this description is a C terminal (carboxyl terminus). Array number: C terminals may be any of a carboxyl group (-COOH), carboxylate (-COO-), an amide (-CONH2), or ester (-COOR) including Homo sapiens RFRP and RFRP who consists of an amino acid sequence expressed with 1.
As R in ester, here, for example Methyl, ethyl, n-propyl, C1-6 alkyl groups, such as isopropyl or n-butyl For example, C3-8 cycloalkyl radicals, such as cyclopentyl and cyclohexyl, For example, C6-12 aryl groups, such as phenyl and alpha-naphthyl For example, the pivaloyloxymethyl radical used widely as ester for taking orally besides C7-14 aralkyl radicals, such as alpha-naphthyl-C1-2 alkyl groups, such as phenyl-C1-2 alkyl groups, such as benzyl and phenethyl, or alpha-naphthyl methyl, is used.
When RFRP has the carboxyl group (or carboxylate) in addition to the C terminal, a carboxyl group is contained in the range of RFRP as used in the field of [what is amidated or esterified] this invention. As ester in this case, the ester of a C terminal described above, for example is used.
To RFRP, the amino group of the amino acid residue (an example, methionine residue) of an amino terminal Furthermore, a protective group What (for example, is protected by C1-6 acyl groups, such as C1-6 alkanoyl, such as a formyl group and an acetyl group, etc.), What the glutamyl radical of the amino terminal which it is cut in the living body and generated pyroglutamic-acid-ized, the substituent on the side chain of the amino acid of intramolecular (for example, -OH, -SH, and the amino group --) A protective group with suitable imidazole group, Indore radical, guanidino radical, etc. Conjugated protein, such as a thing (for example, protected by C1-6 acyl groups, such as C1-6 alkanoyl radicals, such as a formyl group and an acetyl group, etc.) or the so-called glycoprotein which the sugar chain combined, etc. is contained. Hereafter, it may be called RFRP for short including these polypeptides.
[0010]
As an example of RFRP used by this invention For example, an array number : Homo sapiens RFRP who consists of an amino acid sequence expressed with 1 Array number : The cow RFRP which consists of an amino acid sequence expressed with Homo sapiens RFRP who consists of an amino acid sequence expressed with 3, and array number:5 Array number : The mouse RFRP which consists of an amino acid sequence expressed with Latt RFRP who consists of an amino acid sequence expressed with 7, and array number:9 Array number : Latt RFRP who consists of an amino acid sequence expressed with 22 is used. For example, Homo sapiens RFRP who consists of an amino acid sequence expressed with Homo sapiens RFRP who consists of an amino acid sequence expressed with array number:1, and array number:3, an array number: The cow RFRP which consists of an amino acid sequence expressed with 5 is used preferably.

[0011]
As a partial peptide (a RFRP partial peptide may be called hereafter) of RFRP, it may be the above mentioned partial peptide of RFRP, and as long as it has the capacity combined with OT7T022 (array number: the receptor protein which contains the same amino acid sequence identically to the amino acid sequence expressed with 11, or substantially, or its salt) mentioned later, what kind of thing may be used.
Moreover, a RFRP partial peptide is 1-5 (1-3 amino acid carries out deletion preferably) of the amino acid sequence. Or 1-5 amino acid (preferably 1-3 pieces) adds to the amino acid sequence. Or they are 1-5 pieces (1-3 amino acid is inserted preferably) to the amino acid sequence. Or 1-5 (preferably, you may consist of an amino acid sequence by which 1-3 amino acid was permuted from other amino acid, and may consist of an amino acid sequence which combined these deletion, addition, insertion, and a permutation.) of the amino acid sequence
Moreover, the C terminals of a RFRP partial peptide may be any of a carboxyl group (-COOH), carboxylate (-COO-), an amide (-CONH2), or ester (-COOR) (R shows the above and this meaning). Especially, that whose C terminal is an amide (-CONH2) is desirable.
A carboxyl group is contained in the RFRP partial peptide as used in the field of [what is amidated or esterified] this invention when the RFRP partial peptide has the carboxyl group (or carboxylate) in addition to the C terminal. As ester in this case, the ester of a C terminal described above, for example is used.
Furthermore, compound peptides, such as that from which the amino group of the amino acid residue (an example, methionine residue) of an amino terminal is protected by the protective group, a thing which the glutamyl radical which N one end was cut in the living body, and was generated pyroglutamic-acid-ized, a thing protected by the protective group with the suitable substituent on the side chain of the amino acid of intramolecular, or the so-called glycopeptide which the sugar chain combined, etc. are contained like RFRP described above to the RFRP partial peptide. Hereafter, it may be called a RFRP partial peptide for short also including these partial peptides.
The peptide which has RFamide, RSamide, or RLamide structure, the peptide which has RFamide or RSamide structure, and the peptide which has RFamide are mentioned especially more preferably preferably as a RFRP partial peptide. RFamide structure means that the C terminal of ** PUCHIDO has
Arginine(arginine)-Phenylalanine(phenylalanine)-NH2 structure, RSamide structure means that the C terminal of ** PUCHIDO has Arginine(arginine)-Serine(serine)-NH2 structure, and RLamide structure means that the C terminal of ** PUCHIDO has Arginine(arginine)-Leucine(leucine)-NH2 structure.
[0012]
the inside of a RFRP partial peptide -- for example
The 88th - (Leu) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with 3 is contained. (i) -- array number: -- 1 or array number: -- To the amino terminal side of the amino acid sequence respectively -- array number: -- 1 or array number: -- Homo sapiens RFRP-1 which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 87th amino acid sequence (Asn) of the amino acid sequence expressed with 3, and 1-87 amino acid may add,
The 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence

expressed with 3 is contained. (ii) -- array number: -- 1 or array number: -- To the amino terminal side of the amino acid sequence ******** array number: -- 1 or array number: -- Homo sapiens RFRP-2 which consist of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 100th amino acid sequence (Arg) of the amino acid sequence expressed with 3, and 1-100 amino acid may add, The 127th - (Leu) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 3 is contained. (iii) array number: -- 1 or array number: -- To the amino terminal side of the amino acid sequence respectively -- array number: -- 1 or array number: -- Homo sapiens RFRP-3 which consist of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 126th amino acid sequence (Asn) of the amino acid sequence expressed with 3, and 1-126 amino acid may add,
(iv) -- array number: -- cow RFRP-1 which consists of an amino acid sequence which could contain the 88th - (Leu) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with 5, could count from the C terminal of the 1st - (Met) the 87th amino acid sequence (Asn) of the amino acid sequence expressed with array number:5 to the amino terminal side of the amino acid sequence, and 1-87 amino acid may add,
(v) -- array number: -- cow RFRP-2 which consist of an amino acid sequence which could contain the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5, could count from the C terminal of the 1st - (Met) the 100th amino acid sequence (Arg) of the amino acid sequence expressed with array number:5 to the amino terminal side of the amino acid sequence, and 1-100 amino acid may add,
(vi) -- array number: -- cow RFRP-3 which consist of an amino acid sequence which could contain the 127th - (Leu) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 5, could count from the C terminal of the 1st - (Met) the 126th amino acid sequence (Asn) of the amino acid sequence expressed with array number:5 to the amino terminal side of the amino acid sequence, and 1-126 amino acid may add,
Array number: (vii) Mouse RFRP-1 which consists of an amino acid sequence which could contain the 90th - (Leu) the 94th amino acid sequence (Phe) of the amino acid sequence expressed with 9, could count from the C terminal of the 1st - (Met) the 89th amino acid sequence (Asn) of the amino acid sequence expressed with array number:9 to the amino terminal side of the amino acid sequence, and 1-89 amino acid may add,
Array number: (viii) Mouse RFRP-3 which consist of an amino acid sequence which could contain the 121st - (Leu) the 125th amino acid sequence (Phe) of the amino acid sequence expressed with 9, could count from the C terminal of the 1st - (Met) the 120th amino acid sequence (Ser) of the amino acid sequence expressed with array number:9 to the amino terminal side of the amino acid sequence, and 1-120 amino acid may add,
(ix) -- array number: -- the 90th - (Leu) the 94th amino acid sequence (Phe) of the amino acid sequence expressed with 7 or 22 -- containing -- the amino terminal side of the amino acid sequence -- array number: -- Latt RFRP-1 which consists of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 89th amino acid sequence (Asn) of the amino acid sequence expressed with 7 or 22,

and 1-89 amino acid may add,
(x) -- array number: -- the 121st - (Leu) the 125th amino acid sequence (Phe) of the amino acid sequence expressed with 7 or 22 -- containing -- the amino terminal side of the amino acid sequence -- array number: -- Latt RFRP-3 which consist of an amino acid sequence which could count from the C terminal of the 1st - (Met) the 120th amino acid sequence (Ser) of the amino acid sequence expressed with 7 or 22, and 1-120 amino acid may add,
(xi) Peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of above-mentioned (i) - (x),
(xii) The above (i) Peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x),
(xiii) the peptide which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xiv) The peptide which consists of an amino acid sequence which combined addition, insertion, and the permutation of above-mentioned (xi) - (xiii) is used.
[0013]
Even inside of these RFRP partial peptides,
(i) -- array number: -- 1 or array number: -- Homo sapiens RFRP-1 which consists of the 56th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 3, the 70th - (Met) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe)
(ii) -- array number: -- 1 or array number: -- Homo sapiens RFRP-2 which consist of the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3,
(iii) array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 101st - (Asn) 131st (Phe) The 104th - (Asn) 131st (Phe) and the 115th - (Asn) 131st (Phe) Homo sapiens RFRP-3 which consist of the 124th - (Val) 131st (Phe), the 125th - (Pro) 131st (Phe), the 126th - (Asn) 131st (Phe), or the 127th - (Leu) the 131st amino acid sequence (Phe),
(iv) -- array number: -- cow RFRP-1 which consists of the 58th - (Ser) 92nd (Phe) of the amino acid sequence expressed with 5, the 70th - (Lys) 92nd (Phe), the 73rd - (Met) 92nd (Phe), the 81st - (Met) 92nd (Phe), or the 84th - (Ser) the 92nd amino acid sequence (Phe),
(v) -- array number: -- cow RFRP-2 which consist of the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5,
(vi) -- array number: -- the amino acid sequence expressed with 5 the 101st - (Ser) 131st (Phe) The 104th - (Ala) 131st (Phe) and the 115th - (Asn) 131st (Phe) Cow RFRP-3 which consist of the 124th - (Val) 131st (Phe), the 125th - (Pro) 131st (Phe), the 126th - (Asn) 131st (Phe), or the 127th - (Leu) the 131st amino acid sequence (Phe),
Array number: (vii) Mouse RFRP-1 which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 9, the 72nd - (Val) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe),
Array number: (viii) Mouse RFRP-3 which consist of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 9, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),

(ix) -- array number: -- Latt RFRP-1 which consists of the 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 7 or 22, the 72nd - (Asp) 94th (Phe), the 75th - (Met) 94th (Phe), the 83rd - (Val) 94th (Phe), or the 84th - (Pro) the 94th amino acid sequence (Phe),
(x) -- array number: -- Latt RFRP-3 which consist of the 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 7 or 22, the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe),
(xi) Deletion mold peptide with which 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) consists of amino acid sequences which carried out deletion,
(xii) The above (i) Addition mold peptide which consists of an amino acid sequence which 1-5 amino acid added to the amino acid sequence of the peptide of - (x),
(xiii) The above (i) Inserting type peptide which consists of an amino acid sequence by which 1-5 amino acid was inserted in the amino acid sequence of the peptide of - (x),
(xiv) the permutation mold peptide which consists of an amino acid sequence permuted from 1-5 amino acid in the amino acid sequence of the peptide of above-mentioned (i) - (x) -- or
(xv) The peptide which consists of an amino acid sequence which combined the deletion, addition, insertion, and the permutation of above-mentioned (xi) - (xiv) is used preferably.
[0014]
The amide object (peptide with which the carboxyl group (-COOH) of the C terminal of these peptides was amidated preferably (-CONH2)) of these peptides is especially desirable.
The peptide with which the C terminal of a peptide specifically expressed with the 81st - (Met) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with array number:1 was amidated (-CONH2) (array number: 13), Array number : The 101st of the amino acid sequence expressed with 1 (Ser) - the 112nd The C terminal of a peptide expressed with the amino acid sequence of (Ser) Were amidated. A peptide (array number: 15) (-CONH2) And an array number: The peptide (-CONH2) (array number: 14) with which the C terminal of a peptide expressed with the 124th - (Val) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 1 was amidated is raised.
[0015]
The acid addition salt which a salt with an acid (the example, the inorganic acid, organic acid), a base (the example, alkali-metal salt), etc. which are permitted physiologically is used as a salt of RFRP or a RFRP partial peptide, and is especially permitted physiologically is desirable. As such a salt, a salt with an inorganic acid (for example, a hydrochloric acid, a phosphoric acid, a hydrobromic acid, a sulfuric acid) or a salt with an organic acid (for example, an acetic acid, a formic acid, a propionic acid, a fumaric acid, a maleic acid, a succinic acid, a tartaric acid, a citric acid, a malic acid, oxalic acid, a benzoic acid, methansulfonic acid, benzenesulfonic acid) is used, for example.
RFRP, its salt, a RFRP partial peptide, or its salt can be manufactured according to the approach of a publication to WO 00/No. 29441, WO 01/No. 66134, etc.
[0016]
As long as it contains the base sequence which carries out the code of the RFRP

mentioned above as DNA which carries out the code of the RFRP, you may be what kind of thing. Moreover, cDNA of genomic DNA, a genomic DNA library, and the above mentioned above mentioned cell and organization origin, the above mentioned cDNA library of a cell and the organization origin, and any of a synthetic DNA are sufficient. The vectors used for a library may be any, such as a bacteriophage, a plasmid, cosmid, and phagemid. Moreover, it can also amplify using what prepared totalRNA or a mRNA fraction by direct Reverse Transcriptase Polymerase Chain Reaction (it is hereafter called RT-PCR method for short) from above mentioned cell and organization.

[0017]

as DNA which carries out the code of the RFRP -- array number:2 and array number: -- DNA containing the base sequence expressed with 4, array number:6, array number:8, array number:10, or array number:23 -- It has the base sequence hybridized under stringent conditions. or array number: -- 2 and array number: -- the base sequence expressed with 4, array number:6, array number:8, array number:10, or array number:23, and a high -- Array number: Which thing may be used as long as it is DNA which carries out the code of RFRP which consists of an amino acid sequence expressed with 1, array number:3, array number:5, array number:7, array number:9, or array number:22, and the polypeptide which has homogeneous activity substantially. array number: -- 2 and array number: -- the base sequence expressed with 4, array number:6, array number:8, array number:10, or array number:23, and a high -- as DNA which can be hybridized under stringent conditions For example, the base sequence expressed with array number:2, array number:4, array number:6, array number:8, array number:10, or array number:23, respectively, and about 70% or more, DNA containing the base sequence which has about 95% or more of homology still more preferably etc. is used about 90% or more about 80% or more preferably.

The homology of a base sequence can calculate on condition that the following (expected-value = 10;; which allows a gap filtering = ON; match score = 1; mismatch score = -3) using homology computational algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

hybridization -- the very thing -- the approach according to a well-known approach or well-known it -- for example, molecular -- according to the approach of a publication etc., it can carry out to - cloning (Molecular Cloning) 2nd (J.Sambrook et al., Cold Spring Harbor Lab.Press, 1989). Moreover, when using a commercial library, according to the approach of a publication, it can carry out to attached directions for use. more -- desirable -- a high -- it can carry out according to stringent conditions.

Yes, for example, sodium concentration is about 19 to 20 mM preferably about 19 to 40 mM, and, as for stringent conditions, temperature shows preferably about 50-70 degrees C of about 60-65-degree C conditions. Especially, the case where sodium concentration is [temperature] about 65 degrees C in about 19 mM(s) is the most desirable.

[0018]

DNA which consists of a base sequence expressed with array number:2 as DNA which carries out the code of Homo sapiens RFRP who more specifically consists of an amino acid sequence expressed with array number:1 is used. Moreover, an array number: DNA which consists of a base sequence expressed with array number:4 as DNA which carries out the code of Homo sapiens RFRP who consists of an amino acid sequence expressed with 3 is used. Array number: DNA which consists of a base

sequence expressed with array number:6 as DNA which carries out the code of the cow RFRP which consists of an amino acid sequence expressed with 5 is used. Array number: DNA which consists of a base sequence expressed with array number:8 as DNA which carries out the code of Latt RFRP who consists of an amino acid sequence expressed with 7 is used. Array number: DNA which consists of a base sequence expressed with array number:10 as DNA which carries out the code of the mouse RFRP which consists of an amino acid sequence expressed with 9 is used. Array number: DNA which consists of a base sequence expressed with array number:23 as DNA which carries out the code of Latt RFRP who consists of an amino acid sequence expressed with 22 is used.

[0019]

As long as it contains the base sequence which carries out the code of the RFRP partial peptide which mentioned the RFRP partial peptide above as DNA which carries out a code, you may be what kind of thing. Moreover, cDNA of genomic DNA, a genomic DNA library, and the above mentioned above mentioned cell and organization origin, the above mentioned cDNA library of a cell and the organization origin, and any of a synthetic DNA are sufficient.

As DNA which carries out the code of the RFRP partial peptide For example, array number:2, array number:4, array number:6, array number:8, array number:10, or an array number : DNA which has the partial base sequence of DNA containing the base sequence expressed with 23, It has the base sequence hybridized under stringent conditions. or array number: -- 2 and array number: -- the base sequence expressed with 4, array number:6, array number:8, array number:10, or array number:23, and a high -- Array number: DNA which has the partial base sequence of DNA which carries out the code of RFRP which consists of an amino acid sequence expressed with 1, array number:3, array number:5, array number:7, array number:9, or array number:22, and the polypeptide which has homogeneous activity substantially is used.

Array number: The base sequence expressed with 2, array number:4, array number:6, array number:8, array number:10, or array number:23 and DNA which can be hybridized show the above and this meaning.

The homology of a base sequence can calculate on the same conditions using above mentioned homology computational algorithm NCBI BLAST.

the approach of hybridization, and a high -- the thing as the above with the same stringent conditions is used.

[0020]

Moreover, DNA which more specifically as DNA which carries out the code of the RFRP partial peptide carries out the code of the above mentioned concrete RFRP partial peptide is used. For example,

(i) -- array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 56th - (Ser) 92nd (Phe) The 70th - (Met) 92nd (Phe) and the 73rd - (Met) 92nd (Phe) As DNA which carries out the code of the Homo sapiens RFRP-1 which consists of the 81st - (Met) 92nd (Phe) or the 84th - (Ser) the 92nd amino acid sequence (Phe) respectively -- array number: -- 2 or array number: -- DNA which consists of the 166th - 276th of the base sequence expressed with 4, the 208th - 276th, the 217th - 276th, the 241st - 276th, or the 250th - the 276th base sequence,

(ii) -- array number: -- 1 or array number: -- DNA which consists of the 301st - the 336th base sequence of the base sequence expressed with array number:2 or array

number:4, respectively as DNA which carries out the code of the Homo sapiens RFRP-2 which consist of the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 3,
(iii) array number: -- 1 or array number: -- the amino acid sequence expressed with 3 the 101st - (Asn) 131st (Phe) The 104th - (Asn) 131st (Phe) and the 115th - (Asn) 131st (Phe) The 124th - (Val) 131st (Phe) and the 125th - (Pro) 131st (Phe) As DNA which carries out the code of the Homo sapiens RFRP-3 which consist of the 126th - (Asn) 131st (Phe) or the 127th - (Leu) the 131st amino acid sequence (Phe) respectively -- array number: -- 2 or array number: -- the base sequence expressed with 4 the 301st - 393rd DNA which consists of the 310th - 393rd, the 343rd - 393rd, the 370th - 393rd, the 373rd - 393rd, the 376th - 393rd, or the 379th - the 393rd base sequence,
(iv) -- array number: -- the amino acid sequence expressed with 5 the 58th - (Ser) 92nd (Phe) The 70th - (Lys) 92nd (Phe) and the 73rd - (Met) 92nd (Phe) As DNA which carries out the code of the cow RFRP-1 which consists of the 81st - (Met) 92nd (Phe) or the 84th - (Ser) the 92nd amino acid sequence (Phe) Array number: DNA which consists of the 172nd - 276th of the base sequence expressed with 6, the 208th - 276th, the 217th - 276th, the 241st - 276th, or the 250th - the 276th base sequence,
(v) -- array number: -- DNA which consists of the 301st - the 336th base sequence of the base sequence expressed with array number:6 as DNA which carries out the code of the cow RFRP-2 which consist of the 101st - (Ser) the 112nd amino acid sequence (Leu) of the amino acid sequence expressed with 5,
(vi) -- array number: -- the amino acid sequence expressed with 5 the 101st - (Ser) 131st (Phe) The 104th - (Ala) 131st (Phe) and the 115th - (Asn) 131st (Phe) The 124th - (Val) 131st (Phe) and the 125th - (Pro) 131st (Phe) As DNA which carries out the code of the cow RFRP-3 which consist of the 126th - (Asn) 131st (Phe) or the 127th - (Leu) the 131st amino acid sequence (Phe) Array number : The 301st - 393rd of the base sequence expressed with 6 DNA which consists of the 310th - 393rd, the 343rd - 393rd, the 370th - 393rd, the 373rd - 393rd, the 376th - 393rd, or the 379th - the 393rd base sequence,
Array number : The 58th - (Ser) 94th (Phe) of the amino acid sequence expressed with 9 (vii) The 72nd - (Val) 94th (Phe) and the 75th - (Met) 94th (Phe) As DNA which carries out the code of the mouse RFRP-1 which consists of the 83rd - (Val) 94th (Phe) or the 84th - (Pro) the 94th amino acid sequence (Phe) Array number: DNA which consists of the 172nd - 282nd of the base sequence expressed with 10, the 214th - 282nd, the 223rd - 282nd, the 247th - 282nd, or the 250th - the 282nd base sequence,
Array number : The 118th - (Phe) 125th (Phe) of the amino acid sequence expressed with 9 (viii) As DNA which carries out the code of the mouse RFRP-3 which consist of the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe) Array number: DNA which consists of the 352nd - 375th of the base sequence expressed with 10, the 356th - 375th, the 358th - 375th, or the 361st - the 375th base sequence,
(ix) -- array number: -- the amino acid sequence expressed with 7 or 22 the 58th - (Ser) 94th (Phe) The 72nd - (Asp) 94th (Phe) and the 75th - (Met) 94th (Phe) As DNA which carries out the code of the Latt RFRP-1 which consists of the 83rd -

(Val) 94th (Phe) or the 84th - (Pro) the 94th amino acid sequence (Phe) respectively -- array number: -- DNA which consists of the 172nd - 282nd of the base sequence expressed with 8 or 51, the 214th - 282nd, the 223rd - 282nd, the 247th - 282nd, or the 250th - the 282nd base sequence,
(x) -- array number: -- the amino acid sequence expressed with 7 or 22 the 118th - (Phe) 125th (Phe) As DNA which carries out the code of the Latt RFRP-3 which consist of the 119th - (Pro) 125th (Phe), the 120th - (Ser) 125th (Phe), or the 121st - (Leu) the 125th amino acid sequence (Phe) respectively -- array number: -- DNA which consists of the 352nd - 375th of the base sequence expressed with 8 or 51, the 355th - 375th, the 358th - 375th, or the 361st - the 375th base sequence is used.
[0021]
Cloning of DNA which carries out the code of RFRP or its partial peptide thoroughly can be performed to WO 00/No. 29441, WO 01/No. 66134, etc. according to the approach of a publication.
Moreover, when manufacturing RFRP from DNA which carries out the code of RFRP or its partial peptide, or its partial peptide, according to the approach of a publication, it can carry out to WO 00/No. 29441, WO 01/No. 66134, etc.
RFRP or its partial peptide, the below-mentioned OT7T022 or the partial peptide of those, and DNA that carries out the code of these -- the very thing -- it may be labeled by the well-known approach and that by which isotope labeling was specifically carried out, the thing (for example, fluorescent labeling by a fluorescein etc.) by which fluorescent labeling was carried out, the biotin-ized thing, or the thing by which enzyme labeling was carried out is raised.
[0022] As receptor protein OT7T022 (it is hereafter written as OT7T022) to RFRP, its amide, its ester or its salt, a RFRP partial peptide, its amide, its ester, or its salt, the receptor protein which contains the same amino acid sequence identically to the amino acid sequence expressed with array number:11 or substantially is used, for example.
[0023]
OT7T022 -- for example, mammalian (for example, Homo sapiens and a guinea pig --) All cells, such as Latt, a mouse, a rabbit, Buta, a sheep, a cow, and an ape for example, splenic cells, a nerve cell, a neuroglia, a pancreas beta cell, and a bone marrow cell -- A mesangial cell, Langerhans cell, an epidermal cell, an epithelial cell, an endothelial cell, fibrocyte, a desmacyte, a muscle cell, a fat cell, and immunocyte (an example and a macrophage --) A T cell, a B cell, a spontaneous killer cell, a mast cell, neutrophil leucocyte, basophilic leucocyte, Eosinophile leucocyte, monocyte, megakaryocyte, a synovial cell, chondrocyte, osteocyte, osteoblast, An osteoclast, an alveolar epithelial cell, hepatocyte, an interstitial cell, or the precursor cell of these cells, All the organizations where a stem cell or a gun cell, the cells of a corpuscle system, or those cells exist, about (an example, an olfactory bulb, an amygdala, and a cerebrum -- the base -- a ball, a hippocampus, and a thalamus --) each part of a brain and a brain Hypothalamus, a subthalamic nucleus, the cerebral cortex, a medulla oblongata, a cerebellum, an occipital lobe, the frontal lobe, a temporal lobe, Putamen, a caudate nucleus, ****, substantia nigra, a spine, a hypophysis, the stomach, the pancreas, the kidney, liver, a gonad, the thyroid, the gallbladder, bone marrow, a suprarenal gland, the skin, muscles, lungs, and an alimentary canal (an example --) You may be the protein originating in the large intestine, a small intestine, a blood vessel, the heart, a thymus

gland, a spleen, an submaxillary gland, peripheral blood, a peripheral blood ball, a prostate gland, a testis, a testis, the ovary, a placenta, a uterus, a bone, a joint, skeletal muscle (especially each part of a brain or a brain), etc., and may be synthetic protein.
Array number: The amino acid sequence which has about 95% or more of homology most preferably about 90% or more still more preferably about 80% or more as more preferably [preferably / about 70% or more] about 50% or more as the amino acid sequence expressed with array number:11 as the same amino acid sequence, for example as substantially as the amino acid sequence expressed with 11 is mentioned.
[0024]
Array number: It has the same amino acid sequence substantially with the amino acid sequence expressed with 11, and the amino acid sequence expressed with array number:11 as protein which contains the same amino acid sequence substantially, for example, and OT7T022 which consist of an amino acid sequence expressed with array number:11, the receptor protein which has homogeneous activity substantially are desirable, and the receptor protein which specifically consists of an amino acid sequence expressed with array number:24 is raised.
The homology of an amino acid sequence can calculate on condition that the following (expected-value = 10;; which allows a gap matrix = BLOSUM62; filtering = OFF) using homology computational algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool). As homogeneous activity, ligand avidity or a signal signal transduction operation is mentioned substantially, for example. It is substantially indicated to be the same quality that those activity is homogeneous in property. Therefore, although it is desirable that activity, such as ligand avidity or a signal signal transduction operation, is EQCs (an example, about 0.01 to 100 times, preferably about 0.5 to 20 times, more preferably about 0.5 to 2 twice), quantitative elements, such as extent of such activity and proteinic molecular weight, may differ. measurement of activity, such as ligand avidity or a signal signal transduction operation, -- the very thing -- although it can carry out according to a well-known approach, according to the decision approach and the screening approach of ligand which are mentioned later, it can measure, for example.
As OT7T022, moreover, **1 array number: -- 11 or array number: -- the amino acid sequence in which 1 in the amino acid sequence expressed with 24 or two or more (preferably about 1-30 pieces, more preferably about 1-10 pieces, still more preferably partly (1 or two pieces)) amino acid carried out deletion -- **2 array number: -- 11 or array number: -- the amino acid sequence which 1 or two or more (preferably about 1-30 pieces, more preferably about 1-10 pieces, still more preferably partly (1 or two pieces)) amino acid added to the amino acid sequence expressed with 24 -- **3 array number: -- 11 or array number: -- the amino acid sequence by which 1 in the amino acid sequence expressed with 24 or two or more (preferably about 1-30 pieces, more preferably about 1-10 pieces, still more preferably partly (1 or two pieces)) amino acid were permuted from other amino acid -- or **4 The receptor protein which consists of an amino acid sequence which combined these deletion, addition, and a permutation is used.
[0025]
According to the practice of a peptide mark, a left end is an amino terminal (amino terminus), and the right end of OT7T022 in this description is a C terminal (carboxyl

terminus). Array number: The C terminals of OT7T022 including OT7T022 which consist of an amino acid sequence expressed with 11 may be any of a carboxyl group (-COOH), carboxylate (-COO-), an amide (-CONH2), or ester (-COOR).
As R in ester, here, for example Methyl, ethyl, n-propyl, C1-6 alkyl groups, such as isopropyl or n-butyl For example, C3-8 cycloalkyl radicals, such as cyclopentyl and cyclohexyl, For example, C6-12 aryl groups, such as phenyl and alpha-naphthyl For example, the pivaloyloxymethyl radical used widely as ester for taking orally besides C7-14 aralkyl radicals, such as alpha-naphthyl-C1-2 alkyl groups, such as phenyl-C1-2 alkyl groups, such as benzyl and phenethyl, or alpha-naphthyl methyl, is used.
[0026]
When OT7T022 have the carboxyl group (or carboxylate) in addition to the C terminal, that by which the carboxyl group is amidated or esterified is also contained in the range of OT7T022. As ester in this case, the ester of a C terminal described above, for example is used.
In OT7T022 described above to OT7T022 the amino group of the methionine residue of an amino terminal Furthermore, a protective group What (for example, is protected by C1-6 acyl groups, such as C2-6 alkanoyl radicals, such as a formyl group and acetyl, etc.), What the glutamyl radical which N one end was cut in the living body, and was generated pyroglutamic-acid-ized, the substituent on the side chain of the amino acid of intramolecular (for example, -OH, -SH, and the amino group --) Conjugated protein, such as a thing from which the imidazole group, the Indore radical, the guanidino radical, etc. are protected by suitable protective groups (for example, C1-6 acyl groups, such as C2-6 alkanoyl radicals, such as a formyl group and acetyl, etc.), or the so-called glycoprotein which the sugar chain combined, etc. is contained.
Latt OT7T022, an array number which consist of an amino acid sequence expressed with array number:11 as an example of OT7T022, for example: Homo sapiens OT7T022 which consist of an amino acid sequence expressed with 24 are used.
[0027]
Although you may be which thing as long as it is the above mentioned partial peptide of OT7T022 as a partial peptide of OT7T022, it is the part exposed out of a cell membrane among OT7T022 protein molecules, and what has receptor avidity is used, for example.
It is a peptide containing the part analyzed to be an extracellular field (hydrophilic (Hydrophilic) part) in hydrophobic plot analysis as a partial peptide of OT7T022 which specifically consists of an amino acid sequence expressed with array number:11 or array number:24. Moreover, the peptide which includes a hydrophobic (Hydrophobic) part in a part can be used similarly. Although the peptide which includes each domain according to an individual can also be used, the peptide of the part which includes two or more domains simultaneously is sufficient.
The number of the amino acid of the partial peptide of OT7T022 has [at least 20 or more in the above mentioned configuration amino acid sequence of OT7T022] the preferably desirable peptide which consists of 100 or more amino acid sequences more preferably 50 or more pieces.
Moreover, the partial peptide of OT7T022 is 1 in the above-mentioned amino acid sequence, or two pieces or more (preferably). Amino acid [some (1 or two pieces) still more preferably] carries out deletion of the about 1-10 pieces. Or it is 1 or two

pieces or more (preferably) to the amino acid sequence. About 1-20 amino acid [some (1 or two pieces) still more preferably] adds about 1-10 pieces more preferably. Or 1 in the amino acid sequence or two or more (preferably about 1-10 pieces, more preferably partly (1 or two pieces)) amino acid may be permuted by other amino acid. Moreover, the C terminals of the partial peptide of OT7T022 may be any of a carboxyl group (-COOH), carboxylate (-COO-), an amide (-CONH2), or ester (-COOR) (R shows the above and this meaning).
When the partial peptide of OT7T022 has the carboxyl group (or carboxylate) in addition to the C terminal, that by which the carboxyl group is amidated or esterified is also contained in the range of OT7T022. As ester in this case, the ester of a C terminal described above, for example is used.
Furthermore, compound peptides, such as that from which the amino group of the methionine residue of an amino terminal is protected by the protective group, a thing which the glutamyl radical which N one end was cut in the living body, and was generated pyroglutamic-acid-ized, a thing protected by the protective group with the suitable substituent on the side chain of the amino acid of intramolecular, or the so-called glycopeptide which the sugar chain combined, etc. are contained like OT7T022 described above to the partial peptide of OT7T022.
The acid addition salt especially physiologically permitted as a salt of OT7T022 or the partial peptide of those is desirable. As such a salt, a salt with an inorganic acid (for example, a hydrochloric acid, a phosphoric acid, a hydrobromic acid, a sulfuric acid) or a salt with an organic acid (for example, an acetic acid, a formic acid, a propionic acid, a fumaric acid, a maleic acid, a succinic acid, a tartaric acid, a citric acid, a malic acid, oxalic acid, a benzoic acid, methansulfonic acid, benzenesulfonic acid) is used, for example.
OT7T022 or the salt of those and the cell that discovers OT7T022, or its cell membrane fraction can be manufactured according to the approach of a publication to WO 00/No. 29441, WO 01/No. 66134, etc.
[0028]
As long as it contains the base sequence (DNA or RNA, preferably DNA) which carries out the code of OT7T022 as a polynucleotide which carries out the code of OT7T022, you may be what kind of thing. As this polynucleotide, it may be RNA which carries out the code of OT7T022, such as DNA and mRNA, and may be a double strand, or you may be a single strand. In the case of a double strand, the hybrid of double stranded DNA, double stranded RNA, or DNA:RNA is sufficient. In the case of a single strand, it may be a sense chain (namely, code chain), or it may be an antisense strand (namely, non-code chain).
The quantum of the mRNA of OT7T022 can be carried out by the approach according to the approach of well-known experimental-medicine special number "new PCR and its application" 15(7) and 1997 publications, or it, using the polynucleotide which carries out the code of OT7T022.
As DNA which carries out the code of OT7T022, cDNA of genomic DNA, a genomic DNA library, and the above mentioned above mentioned cell and organization origin, the above mentioned cDNA library of a cell and the organization origin, and any of a synthetic DNA are sufficient. The vectors used for a library may be any, such as a bacteriophage, a plasmid, cosmid, and phagemid. Moreover, it can also amplify using what prepared totalRNA or a mRNA fraction by direct Reverse Transcriptase

Polymerase Chain Reaction (it is hereafter called RT-PCR method for short) from above mentioned cell and organization.

[0029]

As DNA which carries out the code of OT7T022, specifically For example, array number:12, array number:25, or an array number : DNA containing the base sequence expressed with 26, It has the base sequence hybridized under stringent conditions. or array number: -- the base sequence expressed with 12, array number:25, or array number:26, and a high -- array number: -- 11 or array number: -- which thing may be used as long as it is DNA which carries out the code of the receptor protein which has homogeneous activity (an example, ligand avidity, signal signal transduction operation, etc.) substantially to OT7T022 which consist of an amino acid sequence expressed with 24.

Array number: DNA containing the base sequence which has about 95% or more of homology most preferably etc. is used about 90% or more more preferably about 80% or more as preferably about 70% or more as the base sequence expressed with 12, array number:25, or array number:26, and the base sequence expressed with array number:12, array number:25, or array number:26 as DNA which can be hybridized, for example.

The homology of a base sequence can calculate on condition that the following (expected-value = 10;; which allows a gap filtering = ON; match score = 1; mismatch score = -3) using homology computational algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

hybridization -- the very thing -- the approach according to a well-known approach or well-known it -- for example, molecular -- according to the approach of a publication etc., it can carry out to - cloning (Molecular Cloning) 2nd (J.Sambrook et al., Cold Spring Harbor Lab.Press, 1989). Moreover, when using a commercial library, according to the approach of a publication, it can carry out to attached directions for use. more -- desirable -- a high -- it can carry out according to stringent conditions.

this high -- for example, sodium concentration is about 19 to 20 mM preferably about 19 to 40 mM, and, as for stringent conditions, temperature shows preferably about 50-70 degrees C of about 60-65-degree C conditions. Especially, the case where sodium concentration is [temperature] about 65 degrees C in about 19 mM(s) is the most desirable.

DNA which consists of a base sequence expressed with array number:12 as DNA which carries out the code of the Latt OT7T022 which more specifically consist of an amino acid sequence expressed with array number:11 is used. Array number: DNA which consists of a base sequence expressed with array number:25 or array number:26 as DNA which carries out the code of the Homo sapiens OT7T022 which consist of an amino acid sequence expressed with 24 is used.

[0030]

As long as it contains the base sequence which carries out the code of the partial peptide of OT7T022 which mentioned above the partial peptide of OT7T022 as DNA which carries out a code, you may be what kind of thing. Moreover, cDNA of genomic DNA, a genomic DNA library, and the above mentioned above mentioned cell and organization origin, the above mentioned cDNA library of a cell and the organization origin, and any of a synthetic DNA are sufficient. The vectors used for a library may be any, such as a bacteriophage, a plasmid, cosmid, and phagemid. Moreover, it can

also amplify using what prepared the mRNA fraction by direct Reverse Transcriptase Polymerase Chain Reaction (it is hereafter called RT-PCR method for short) from above mentioned cell and organization.
As DNA which carries out the code of the partial peptide of OT7T022, specifically For example, (1) array number:12, array number:25, or an array number : DNA which has the partial base sequence of DNA which has the base sequence expressed with 26, It has the base sequence hybridized under stringent conditions. or (2) array number: -- the base sequence expressed with 12, array number:25, or array number:26, and a high -- array number: -- 11 or array number: -- OT7T022 which consist of an amino acid sequence expressed with 24 -- substantial -- homogeneous activity (an example --) DNA which has the partial base sequence of DNA which carries out the code of the receptor protein which has ligand avidity or a signal signal transduction operation is used.
When manufacturing OT7T022 or the partial peptide of those from DNA which carries out the code of OT7T022 or the partial peptide of those, according to the approach of a publication, it can carry out to WO 00/No. 29441, WO 01/No. 66134, etc.
[0031]
the antibody to RFRP, its partial peptide, its amide, its ester, or its salt -- the very thing -- according to the approach of a publication, it can be manufactured and used for the well-known approach 00/No. 29441, for example, WO, WO 01/No. 66134, etc. the antibody to OT7T022, the partial peptide of those, or its salt -- the very thing -- according to the approach of a publication, it can be manufactured and used for the well-known approach 00/No. 29441, for example, WO, WO 01/No. 66134, etc.
[0032]
It not only includes DNA which carries out the code of RFRP or the partial peptide of OT7T022 described above as the polynucleotide which comes to contain a part of a part of base sequence of DNA which carries out the code of RFRP or OT7T022, or this DNA and complementary base sequence, but it is used in the semantics which also includes RNA.
If this invention is followed, the antisense polynucleotide (nucleic acid) which can check the duplicate or manifestation of a RFRP gene or OT7T022 gene was cloned, or determined RFRP or OT7T022 are designed based on the base sequence information on DNA which carries out a code, and can be compounded. Such a polynucleotide (nucleic acid) can be hybridized with RNA of a RFRP gene or OT7T022 gene, it can check composition or the function of this RNA, or can mind an interaction with the RFRP relation RNA or the OT7T022 relation RNA, and can adjust and control a RFRP gene or OT7T022 gene expression. Out of [in-the-living-body and] a living body, a polynucleotide complementary in the array as which the RFRP relation RNA or the OT7T022 relation RNA was chosen and the RFRP relation RNA or the OT7T022 relation RNA, and the polynucleotide that can be hybridized specifically are useful, although a RFRP gene or OT7T022 gene expression is adjusted and controlled, and it is useful to the therapy or diagnosis of a disease etc. it has homology in a nucleotide including a gene [vocabulary / "it corresponds"], a base sequence, or the specific array of a nucleic acid -- it is -- it is -- a complementary thing is meant. The finger of the amino acid of the peptide (protein) in the command guided from the array or its phase complement of the nucleotide (nucleic acid) "corresponds" between a nucleotide, a base sequence or a nucleic acid, and a peptide (protein) is usually carried

out. Although a 5 'edge hairpin loop and 5' edge 6-base pair repeat, 5 'edge untranslation region, polypeptide translation initiation codon, protein coding region, ORF translation initiation codon, and 3' edge untranslation region, and 3 'edge palindrome field and 3' edge hairpin loop of OT7T022 gene can be chosen as a desirable object domain, any fields in a RFRP gene or OT7T022 gene can be chosen as an object.

[0033]

It can be said that the relation between the object nucleic acid and the polynucleotide which it is complementary to a part of object domain [at least], and can be hybridized to it is an object and antisense ["antisense one"]. The polydeoxyribonucleotide in which the antisense polynucleotide contains the 2-deoxy-D-ribose, The polynucleotide of the type of others which are the polyribonucleotide containing D-ribose, a pudding, or N-glycoside of a pyrimidine base, Or the polymer of others containing the polymer (for example, a commercial protein nucleic acid and a commercial synthetic array specific nucleic-acid polymer) of others which have a non-nucleotide frame, or special association (However, this polymer contains a nucleotide with the arrangement which permits pairing of a base and adhesion of a base which are found out in DNA or RNA) etc. -- it is mentioned. They The double stranded DNA, a single stranded DNA, the 2 chain RNA, single stranded RNA, Furthermore, it can be a DNA:RNA hybrid. Further A non-modified polynucleotide (or non-modified oligonucleotide), That to which still better known qualification was added, for example, a thing with the indicator known for the field concerned, that to which the cap was attached, the methylated thing, and one or more natural nucleotides -- a relative -- what was permuted by the object -- That to which intramolecular nucleotide qualification was carried out, for example, non-electrification association A phospho RUAMI date for example, methyl phosphonate and phospho triester -- A thing with a carbamate etc., association which has a charge, or sulfur content association What (for example, has phosphorothioate, phosphorodithioate, etc.), for example, protein (nuclease, nuclease inhibitor, and toxin --) What has side chain radicals, such as an antibody, transit peptide, poly-L-lysine, etc. and sugar (for example, mono-saccharide etc.), A thing with INTAKARENTO compounds (for example, an acridine, PUSORAREN, etc.), You may have the thing containing chelate compounds (for example, a metal, a metal with radioactivity, boron, the metal of an oxidizing quality, etc.), a thing containing an alkylating agent, and embellished association (for example, nucleic acid of alpha anomer mold etc.). It not only contains a pudding and a pyrimidine base, but what has the heterocycle mold base of others which were embellished may be included with the "nucleoside", the "nucleotide", and the "nucleic acid" here. Such a qualification object may include the heterocycle of the methylated pudding and a pyrimidine, the acylated pudding and a pyrimidine, or others. A part for a sugar part may be embellished again, for example, one or more hydroxyl groups may be permuted by the halogen, the aliphatic series radical, etc., or the embellished nucleotide and the embellished nucleotide may be changed into functional groups, such as the ether and an amine.

[0034]

The antisense polynucleotide (nucleic acid) of this invention is RNA, DNA, or the embellished nucleic acid (RNA, DNA). Although the thing of resistance is mentioned to decomposition of the sulfur derivative, thio phosphate derivative and the poly

nucleoside amide of a nucleic acid, or an oligo nucleoside amide as an example of the embellished nucleic acid, it is not limited to it. The antisense nucleic acid of this invention is designed preferably, and is sold at the following policies. That is, supposing toxicity makes bigger compatibility over the sense chain which makes intracellular antisense nucleic acid more stable, which raises the cell permeability of antisense nucleic acid more and which is made into a target, the toxicity of antisense nucleic acid will be made into a smaller thing.
in this way, many qualification is got to know in the field concerned -- having -- **** -- for example, -- J.Kawakami et al., Pharm Tech Japan, Vol.8, pp.247, and 1992; Vol.8, pp.395, and 1992; S.T.Crooke et al.ed., Antisense Research and Applications, CRC Press, and 1993 etc. -- there is disclosure.
The antisense nucleic acid of this invention is made to change, or may contain the embellished sugar, a base, and association, and a grant is made with liposome and a special gestalt like a microsphere, it is applied by gene therapy, or it may be given with the added gestalt. In this way, an interaction with a poly cation object like the poly lysine which works as what is used with an addition gestalt so that the charge of a phosphoric-acid radical frame may be neutralized, and a cell membrane is raised, or a thing of rough aquosity called lipids (for example, phospholipid, cholesterol, etc.) which make the incorporation of a nucleic acid increase is mentioned. As a desirable lipid, cholesterol and its derivatives (for example, cholesteryl chloro formate, cholic acid, etc.) are mentioned for adding. Such a thing can be made to adhere to 3 'edge or 5' edge of a nucleic acid, and may be made to adhere through a base, sugar, and intramolecular nucleoside association. As other radicals, it is the radical for a cap arranged specifically, and the thing for preventing decomposition by nucleases, such as exonuclease and RNase, is mentioned to 3 'edge or 5' edge of a nucleic acid. Although the protective group of the hydroxyl group known for the fields concerned including glycols, such as a polyethylene glycol and tetraethylene glycol, is mentioned as a radical for such a cap, it is not limited to it.
The inhibition activity of antisense nucleic acid can be investigated using the gene expression system besides the transformant of this invention, and in the living body [of this invention] and a living body, or the translation system besides in the living body [of G protein conjugation mold receptor protein], or a living body. this nucleic acid -- it is applicable to a cell by various kinds of well-known approaches in itself.
[0035]
siRNA (siRNA of the following and this invention) to the polynucleotide which carries out the code of RFRP or OT7T022 is double stranded RNA which contains complementary RNA in a part of RNA and it which carry out the code of RFRP or OT7T022.
siRNA can be designed and manufactured based on the array of the polynucleotide of this invention according to a well-known approach (an example, Nature, 411 volumes, 494 pages, and 2001).
The ribozyme containing a part of RNA which carries out the code of RFRP or OT7T022 can be designed and manufactured based on the array of the polynucleotide of this invention according to a well-known approach (an example, TRENDS in Molecular Medicine, seven volumes, 221 pages, and 2001). For example, it can manufacture by permuting a part of array of a well-known ribozyme by a part of RNA which carries out the code of RFRP or OT7T022. The array near the consensus

sequence NUX (N shows all bases among a formula and X shows bases other than G) which may be cut by the well-known ribozyme as a part of RNA which carries out the code of RFRP or OT7T022 etc. is mentioned.

[0036]

RFRP and OT7T022 OT7T022 from the phenotype of the nonhuman mammal which suffered a loss so that it may mention later For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) The increment in the amount of spontaneous behavior, muscular power lowering, etc. were found by participating in an increment or muscular power lowering of the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior) etc. especially at night. Therefore, **1 RFRP, its partial peptide, its amide, its ester or its salt (it is hereafter written as RFRP), **2 DNA, **3 which carry out the code of the RFRP The antibody, **4 to RFRP The antisense DNA, **5 to DNA which carries out the code of the RFRP OT7T022, the partial peptide of those or its salt (it is written as OT7T022), **6 DNA, **7 which carry out the code of OT7T022 The antibody, **8 to OT7T022 The antisense DNA to DNA which carries out the code of OT7T022 has the following applications.

[0037]

(1) Prevention and therapy / improvement agent of the disease relevant to the malfunction of RFRP

a) DNA which carries out the code of DNA which carries out the code of RFRP and the bRFRP, cOT7T022, or dOT7T022 can be used as remedies, such as RFRP or prevention and therapy / improvement agent of the disease relevant to the malfunction of OT7T022.

For example, since RFRP or OT7T022 are decreasing in in the living body When there is a patient who cannot expect RFRP or the function of OT7T022 a) by medicating this patient with RFRP, filling up the amount of this RFRP or making this patient prescribe for the patient and discover DNA which carries out the code of DNA which carries out the code of b (b) RFRP, or OT7T022 Or after inserting in the cell used as a (b) object DNA which carries out the code of DNA which carries out the code of the RFRP, or OT7T022 and making it discovered, by transplanting this cell to this patient etc. RFRP in a patient's inside of the body or the amount of OT7T022 can be made to be able to increase, and RFRP or the function of OT7T022 can fully be demonstrated. namely, DNA which carries out the code of DNA which carries out the code of the RFRP, or OT7T022 -- safe -- low -- it is useful as prevention and/or the therapy agent of the disease relevant to toxic RFRP or the malfunction of OT7T022.

DNA which specifically carries out the code of DNA which carries out the code of aRFRP and the bRFRP, cOT7T022, or dOT7T022 For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function

failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) The increment in the amount of spontaneous behavior, muscular power lowering, etc. can be especially used at night as a prevention and therapy / improvement agent of the increment in the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power lowering.

When using RFRP or OT7T022 as the above-mentioned prevention and therapy / improvement agent, it can pharmaceutical-preparation-ize according to a stock-in-trade.

When using DNA which, on the other hand, carries out the code of DNA which carries out the code of the RFRP, or OT7T022 as the above-mentioned prevention and therapy / improvement agent, after inserting these DNA in suitable independent or vectors, such as a retrovirus vector, an adenovirus vector, and an adenovirus-associated virus vector, it can carry out according to a stock-in-trade. DNA remains as it is or can be prescribed for the patient with a catheter like a gene gun or a hydro gel catheter with the adjuvant for acceleration of intake.

For example, DNA which carries out the code of DNA which carries out the code of aRFRP and the bRFRP, cOT7T022, or dOT7T022 can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as the tablet and capsule which gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with DNA which carries out the code of DNA which carries out the code of aRFRP and the bRFRP, cOT7T022, or dOT7T022 with the unit dosage gestalt required of the pharmaceutical preparation implementation generally accepted with the well-known support which can be accepted physiologically, a flavor agent, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. Capacity with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained.

[0038]

As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into the ingredient of the above-mentioned type. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc. As aquosity liquid for injection, the isotonic solutions (for example, D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the adjuvant of a physiological saline, grape sugar, or others etc. are used, for example, and you may use together with a suitable solubilizing agent (an example, ethanol), for example, alcohol, polyalcohol (an example, propylene glycol, polyethylene glycol), a nonionic surfactant (an example, polysorbate

80 TM, HCO-50), etc. As oily liquid, sesame oil, soybean oil, etc. are used and you may use together with benzyl benzoate, benzyl alcohol, etc. which are a solubilizing agent, for example.

[0039]

Moreover, the above-mentioned prevention and therapy / improvement agent may blend with a buffer (for example, a phosphate buffer, the sodium acetate buffer solution), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution.

Thus, the pharmaceutical preparation obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to Homo sapiens or mammalians (for example, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example.

Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in a nociception failure patient, about 0.1-100mg per day of about 1.0-50mg of doses of RFRP is about 1.0-20mg more preferably (as weight of 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / a nociception failure patient (as the weight of 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in a nociception failure patient, about 0.1-100mg per day of about 1.0-50mg of doses of DNA is about 1.0-20mg more preferably (as weight of 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / a nociception failure patient (as the weight of 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

[0040]

(2) Gene-diagnosis agent

The antisense DNA to DNA which carries out the code of the RFRP, DNA which carries out the code of OT7T022, or these DNA By using it as a probe, Homo sapiens or mammalian Since the abnormalities (abnormality of the genes) of DNA which carries out the code of RFRP [(in / for example, / Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape), etc.] or OT7T022, or mRNA are detectable For example, it is useful as gene-diagnosis agents, such as breakage on this DNA or mRNA, mutation or manifestation lowering, and an increment in this DNA or mRNA or excess of a manifestation.

The above-mentioned gene diagnosis using DNA or an antisense DNA for example, the very thing -- well-known Northern hybridization and the PCR-SSCP method

(Genomics (Genomics) --) The 5th volume, 874-879 pages (1989), Pro C JINGUZU OBU THE National academy OBU sciences OBU U.S.A. () [Proceedings of the National Academy of Sciences of the] It can carry out by United States of America, the 86th volume, 2766-2770 etc. pages (1989), etc.
For example, it can be diagnosed that possibility of falling ill in the future or possibility of being RFRP, the malfunction of OT7T022, or a disease relevant to a superfluous manifestation is high is high when RFRP, manifestation lowering of OT7T022, or an overmanifestation is detected by Northern hybridization.
As RFRP, the malfunction of OT7T022, or a disease relevant to a superfluous manifestation For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, temperature change, white blood cell count change, platelet count change, the amount of spontaneous behavior (especially) Change of the amount of spontaneous behavior, muscular power change, etc. are especially mentioned for the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, change of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power change at night.
As a disease relevant to RFRP or the malfunction of OT7T022, especially For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) The increment in the amount of spontaneous behavior, muscular power lowering, etc. are especially mentioned for the increment in the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), muscular power lowering, etc. at night.
On the other hand, as a disease relevant to RFRP or the superfluous manifestation of OT7T022, the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), a pain, morphine resistance especially the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), etc. are mentioned, for example.
[0041]
(3) The remedy containing the compound to which RFRP or the amount of manifestations of OT7T022 is changed, or its salt
DNA which carries out the code of RFRP or OT7T022 can be used for screening of the compound to which RFRP or the amount of manifestations of OT7T022 is changed, or its salt by using as a probe.
That is, the screening approach of the compound to which RFRP or the amount of

manifestations of OT7T022 by this invention measuring RFRP or the amount of mRNA(s) of OT7T022 contained in a blood, borganization [which isolated from the specific organ and c organ], cell, or (ii) transformant, etc. of for example, the (i) nonhuman mammal is changed, or its salt is offered.

[0042]

Measurement of RFRP or the amount of mRNA(s) of OT7T022 is specifically performed as follows.

(i) As opposed to normal or disease model nonhuman mammals (for example, more specifically [a mouse, Latt, a rabbit, a sheep, Buta a cow, a cat, a dog, an ape, etc.] an immune disorder model rat, a mouse, a rabbit, etc.) Drugs (for example, immunomodulator etc.) or physical stress (For example, flooding stress, an electroshock, light and darkness, low temperature, etc.) etc. -- after giving and carrying out fixed time amount progress, the organization which isolated from blood, specific organs (for example, a brain, liver, the kidney, etc.), or an organ, or a cell is obtained.

RFRP contained in the obtained cell, or mRNA of OT7T022 -- for example, the thing for which mRNA is extracted from a cell etc. by the usual approach, for example, technique, such as TaqMan PCR, is used -- a quantum -- it can carry out -- the very thing -- it is also analyzable by performing a Northern blot with a well-known means.

(ii) The transformant which discovers RFRP or OT7T022 is produced [WO 00/No. 29441 or WO / 01/No. 66134] according to the approach of a publication, and a quantum and analyzing can do similarly RFRP contained in this transformant, or mRNA of OT7T022.

[0043]

Screening of the compound to which RFRP or the amount of manifestations of OT7T022 is changed, or its salt,

(i) Before fixed time amount which gives drugs or physical stress to normal or a disease model nonhuman mammal (30 quotas - 24 hours ago) It is 1 hour before - 6 hours ago or after fixed time amount (after 30 minutes - three days after) more preferably 30 quotas - 12 hours ago. More preferably 1 hour after - two days after 1 hour after - 24 hours after, Or drugs or physical stress, and coincidence are medicated with a trial compound, and it is after after [administration] fixed time amount progress (after 30 minutes - three days after). RFRP or the amount of mRNA(s) of OT7T022 contained in a cell can be preferably performed a quantum and by analyzing 1 hour after - 24 hours after 1 hour after - two days after,

(ii) In case a transformant is cultivated according to a conventional method, a trial compound can be mixed in a culture medium, and RFRP or the amount of mRNA(s) of OT7T022 contained in this transformant can be performed a quantum and by analyzing after fixed time amount culture (one day after - three days after [One day after - seven days after preferably] more preferably two days after - three days after).

As a trial compound, a peptide, protein, a nonpeptidic compound, a synthetic compound, a fermentation product, a cell extract, a vegetable extract, an animal tissue extract, plasma, etc. may be used, and these compounds may be new compounds and may be well-known compounds, for example.

A trial compound has the desirable acid addition salt which the salt may be formed, and a salt with acids (the example, inorganic acid, etc.), bases, etc. (an example, organic acid, etc.) which are permitted physiologically is used as a salt of a trial

compound, and is especially permitted physiologically. As such a salt, a salt with inorganic acids (for example, a hydrochloric acid, a phosphoric acid, a hydrobromic acid, a sulfuric acid, etc.) or a salt with organic acids (for example, an acetic acid, a formic acid, a propionic acid, a fumaric acid, a maleic acid, a succinic acid, a tartaric acid, a citric acid, a malic acid, oxalic acid, a benzoic acid, methansulfonic acid, benzenesulfonic acid, etc.) is used, for example. [0044]

The compound obtained using the screening approach of this invention, or its salt They are the compound which has the operation which changes RFRP or the amount of manifestations of OT7T022, or its salt. Specifically By making (b) RFRP or the amount of manifestations of OT7T022 increase Cell stimulus activity through OT7T022 (for example, arachidonic acid isolation) Acetylcholine isolation, intracellular calcium2+ isolation, intracellular cAMP generation, intracellular cAMP generation control, Intracellular cGMP generation, inositol phoshate production, cell membrane potential fluctuation, the phosphorylation of intracellular protein, They are the compound which decreases this cell stimulus activity, or its salt by decreasing the compound which reinforces the activity which promotes activation of c-fos, lowering of pH, etc., or the activity to control or its salt, and the amount of manifestations of (b) RFRP.

As a compound obtained using the screening approach of this invention, a peptide, protein, a nonpeptidic compound, a synthetic compound, a fermentation product, a cell extract, a vegetable extract, an animal tissue extract, plasma, etc. may be mentioned, and these compounds may be new compounds and may be well-known compounds. The thing same as a salt of this compound as the above mentioned salt of RFRP is used.

The compound to which RFRP or the amount of manifestations of OT7T022 obtained by the above-mentioned screening approach is made to increase, or its salt For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, temperature change, white blood cell count change, platelet count change, the amount of spontaneous behavior (especially) Preferably change of the amount of spontaneous behavior, muscular power change, etc. at night The myonosus, adrenal insufficiency, A convulsion, aggression action, a gait abnormality, temperature change, white blood cell count change, platelet count change, Change of the amount of spontaneous behavior (especially night the amount of spontaneous behavior) or muscular power change, especially the myonosus, It can use as a **** [which it is safe and is low toxicity] and therapy / improvement agent to the increment in adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), and muscular power lowering.

The compound which decreases RFRP or the amount of manifestations of OT7T022 obtained by the above-mentioned screening approach, or its salt can be used as **** [which it is safe and is low toxicity] and therapy / improvement agent to reduction of the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous

behavior (especially night the amount of spontaneous behavior), a painkiller, the analgesic action accelerator of morphine, a morphine resistance evasion agent, a morphine dependency evasion agent, etc.

[0045]

When using the compound obtained using the screening approach of this invention, or its salt as a remedy constituent, it can pharmaceutical-preparation-ize according to a stock-in-trade. It can manufacture like prevention and therapy / improvement agent which specifically contains the above-mentioned RFRP.

The pharmaceutical preparation obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to Homo sapiens or mammalians (for example, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example.

Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally, about 0.1-100mg of about 1.0-50mg of doses of this compound or its salt is about 1.0-20mg more preferably about the compound to which RFRP or the amount of manifestations of OT7T022 is made to increase per day in a nociception failure patient, or its salt (as weight of 60kg).

Although a dose changes with the object organ for administration, a symptom, medication methods, etc. once [the] when prescribing a medicine for the patient parenterally For example, in the form of injections, it usually sets to a nociception failure patient, for example (as weight of 60kg). It is convenient to prescribe more preferably about about 0.01-30mg about about 0.1-20mg about about 0.1-10mg for the patient for the compound to which RFRP or the amount of manifestations of OT7T022 is made to increase per day, or its salt by the intravenous injection. The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

[0046]

(4) The diagnostic approach using an antibody

Since RFRP or the antibody (it is hereafter written as the antibody of this invention) to OT7T022 can recognize RFRP or OT7T022 specifically, it is applicable to RFRP in sample liquid, or detection and neutralization of OT7T022.

Namely, this invention,

(i) -- RFRP in the sample liquid characterized by measuring labeled RFRP which the antibody of this invention, and sample liquid and labeled RFRP or OT7T022 were made to react competitively, and was combined with this antibody, or the rate of OT7T022, or the assay of OT7T022 -- and

(ii) After making the antibody of this invention which insolubilized on sample liquid and support, and another antibody of labeled this invention react simultaneous or continuously, RFRP in the sample liquid characterized by measuring the activity of the indicator agent on insolubilization support or the assay of OT7T022 is offered.

[0047]

In the assay of the above (ii), one antibody is an antibody which recognizes RFRP or N edge of OT7T022, and it is desirable that it is the antibody to which the antibody of another side reacts to RFRP or C edge of OT7T022.

Moreover, RFRP or the quantum of OT7T022 can be performed using RFRP or the monoclonal antibody (monoclonal antibody of the following and this invention) to OT7T022, and also detection by organization dyeing etc. can also be performed. The

antibody molecule itself may be used for these objects, and F(ab') 2, Fab', or the Fab fraction of an antibody molecule may be used for them.
Especially RFRP or the assay of OT7T022 using the antibody of this invention should not be restricted, and as long as it is chemical or a measuring method computed from the standard curve which detected by the physical means and produced this using the standard solution containing the antigen of a known amount about the amount of the antibody corresponding to the amount of antigens in measured liquid (for example, the amount of RFRP(s) or OT7T022 amount), an antigen, or the antibody-antigenic complex, which measuring method may be used for it. For example, although a nephrometry, the competing method, an immunometric method, and a sandwich technique are used suitably, it is desirable especially to use the sandwich technique mentioned later in respect of sensibility and singularity.
[0048]
As an indicator agent used for the measuring method using a marker, radioisotope, an enzyme, a fluorescent material, photogene, etc. are used, for example. As radioisotope, [125I], [131I], [3H], [14C], etc. are used, for example. As the above-mentioned enzyme, it is stable, and the big thing of specific activity is desirable, for example, the beta-galactosidase, the beta-glucosidase, alkaline phosphatase, a par oxidase, a malate dehydrogenase, etc. are used. As a fluorescent material, fluorescamine, full ORESSEN isothiocyanate, etc. are used, for example. As photogene, luminol, a luminol derivative, luciferin, lucigenin, etc. are used, for example. Furthermore, a biotin-avidin system can also be used for association with an antibody or an antigen, and an indicator agent.
The approach using the chemical bond used for using physical adsorption, and usually insolubilizing and fixing an enzyme etc. in insolubilization of an antigen or an antibody may be used. As support, synthetic resin, such as insoluble polysaccharide, such as agarose, a dextran, and a cellulose, polystyrene, polyacrylamide, and silicon, or glass is raised.
The quantum of the amount of RFRP(s) in sample liquid can be carried out by making sample liquid react to the monoclonal antibody of this invention which insolubilized in the sandwich technique (primary response), making the monoclonal antibody of another this invention which labeled further react (secondary response), and measuring the activity of the indicator agent after ** and on insolubilization support. A primary response and a secondary response may be performed in order of reverse, or may be performed simultaneously, may shift time amount and may perform it. A labeling agent and the approach of insolubilization can apply to above them correspondingly. Moreover, in the immunoassay by the sandwich technique, the number of the antibodies used for the antibody for solid phase or the antibody for indicators does not necessarily need to be one, and they may use the mixture of two or more kinds of antibodies for the object of raising sensitometry.
[0049]
In RFRP by the sandwich technique of this invention, or the measuring method of OT7T022, the antibody in which the part where RFRP or OT7T022 combine the monoclonal antibody of this invention used for a primary response and a secondary response is different from each other is used preferably. That is, when, as for the antibody used for a primary response and a secondary response, the antibody used by the secondary response recognizes RFRP or C edge of OT7T022, the antibody which

the antibody used by the primary response is desirable, and recognizes N edge except C edge is used.
The monoclonal antibody of this invention can be used for gaging systems, for example, the competing method, immunometric methods, or nephrometries other than a sandwich technique etc.
By the competing method, after making the antigen and labelled antigen in sample liquid react competitively to an antibody, an unreacted labelled antigen (F) and the labelled antigen (B) combined with the antibody are separated (B/F separation), either amount of indicators of B and F is measured, and the quantum of the amount of antigens in sample liquid is carried out. The solid phase-ized method using [the 1st antibody] a solid phase-ized antibody as the 2nd antibody using the thing of fusibility is used for this reacting method in B/F separation, using a solid phase-ized antibody as the liquid phase process using the 2nd antibody to a polyethylene glycol and said antibody etc., and the 1st antibody, using a fusibility antibody as an antibody.
In an immunometric method, after separating solid phase and the liquid phase, or making the antigen in sample liquid, and the labeling antibody of an excessive amount react, then adding a solid phase-ized antigen, after carrying out the competitive reaction of the antigen and solid phase-ized antigen in sample liquid to the labeling antibody of a constant rate, and combining an unreacted labeling antibody with solid phase, solid phase and the liquid phase are separated. Next, the amount of indicators of one of phases is measured, and the quantum of the amount of antigens in sample liquid is carried out.
Moreover, in a nephrometry, the amount of the insoluble sediment produced within gel and in the solution as a result of the antigen-antibody reaction is measured. The amounts of antigens in sample liquid are few, and also when only a small amount of sediment is obtained, the laser nephrometry using dispersion of laser etc. is used suitably.
In applying the immunoassay of these each to the quantum approach of this invention, setting out of special conditions, actuation, etc. is not needed. What is necessary is to add the usual technical consideration of this contractor to the usual conditions in each approach, and operation information, and just to build RFRP or the system of measurement of OT7T022. A total theory, a compendium, etc. can be referred to about the detail of these general technical means.
For example, inlet The volume on ** "radioimmunoassay" (Kodansha, Showa 49 issuance), Inlet The volume on ** "** radioimmunoassay" (Kodansha, Showa 54 issuance), the volumes "enzyme immunoassay" (the 2nd edition) (Igaku-Shoin --) for "enzyme immunoassay" (Igaku-Shoin, Showa 53 issuance) Eiji Ishikawa edited by Eiji Ishikawa the volumes "enzyme immunoassay" (the 3rd edition) (Igaku-Shoin --) Showa 57 issuance and for Eiji Ishikawa The Showa 62 issuance, "Methods in ENZYMOLOGY" Vol.70 (Immunochemical Techniques (Part A)), The said document Vol.73 (Immunochemical Techniques (Part B)), The said document Vol.74 (Immunochemical Techniques (Part C)), The said document Vol.84 (Immunochemical Techniques (Part D : Selected Immunoassays)), The said document Vol.92 (Immunochemical Techniques (Part E : Monoclonal Antibodies and General Immunoassay Methods)), said document Vol.121 (above) (Immunochemical Techniques (Part I : Hybridoma Technology and Monoclonal Antibodies)) The Academic Press issuance etc. can be referred to.

Sensibility can improve RFRP or OT7T022 a quantum by using the antibody of this invention as mentioned above.

[0050]

Furthermore, by carrying out the quantum of RFRP or the concentration of OT7T022 using the antibody of this invention When reduction of RFRP or the concentration of OT7T022 is detected For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) Especially the increment in the amount of spontaneous behavior, muscular power lowering, etc. at night The myonosus, adrenal insufficiency, Or it is diseases, such as an increment in a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power lowering, it can be diagnosed that possibility of falling ill in the future is high.

Moreover, when the increment in RFRP or the concentration of OT7T022 is detected, or it is diseases, such as the myonosus, adrenal insufficiency, temperature reduction, an increment in a white blood cell count, an increment in a platelet count or reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), a pain, and morphine resistance, it can be diagnosed that possibility of falling ill in the future is high.

[0051]

(5) The remedy containing the compound to which the compound to which the affinity of RFRP and OT7T022 or signal transfer is changed or the screening approach of the salts (agonist, antagonist, etc.) and the affinity of RFRP and OT7T022, or signal transfer is changed, or its salt

By building the manifestation system of recombinant OT7T022, using OT7T022, and using the receptor joint assay system using this manifestation system For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) At night The increment in the amount of spontaneous behavior, muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, The compound to which the affinity of RFRP useful as prevention and therapy / improvement medicine, such as reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), a pain, and morphine resistance, and OT7T022 or signal transfer is changed (For example, a peptide, protein, a nonpeptidic compound, a synthetic compound, a fermentation product, etc.) Or the salt can be screened efficiently.

(b) OT7T022 are such minded. Cell stimulus activity Isolation for example, arachidonic-acid isolation, acetylcholine isolation, and intracellular calcium2+ --

Intracellular cAMP generation, intracellular cAMP generation control, intracellular cGMP generation, Inositol phoshate production, cell membrane potential fluctuation, the phosphorylation of intracellular protein, the compound (being the so-called --) which has the activity which promotes activation of c-fos, lowering of pH, etc., or the activity to control the compound (being the so-called --) which checks OT7T022 agonist and the cell stimulus activity through (b) OT7T022 OT7T022 antagonist, the compound which reinforces the bonding strength of RFRP (Ha) and OT7T022, or the compound which decreases the bonding strength of (d) RFRP and OT7T022 is contained.

Namely, this invention,

(1) the nociception failure characterized by using RFRP and (or) OT7T022 -- An eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, Adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, depression, uneasy **, A reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, The increment in white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), Muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, the amount of spontaneous behavior (especially) Especially reduction of the amount of spontaneous behavior, a pain, morphine resistance, etc. at night A nociception failure, Adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, The screening approach of prevention and therapy / improvement medicine, such as the increment in a decrease of platelets and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), muscular power lowering, temperature reduction, an increment in a white blood cell count, an increment in a platelet count, and reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior),

(2) The nociception failure characterized by performing the comparison with the case where (i) RFRP, the case where 022 is contacted and OT7T(ii) RFRP, OT7T022, and a trial compound are contacted, An eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, Adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, depression, uneasy **, A reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, The increment in white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), Muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, the amount of spontaneous behavior (especially) Especially reduction of the amount of spontaneous behavior, a pain, morphine resistance, etc. at night A nociception failure, Adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, The increment in a decrease of platelets and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), muscular power lowering, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, and the screening approach of prevention and therapy / improvement medicine reduction of the amount of spontaneous behavior (especially night the amount of spontaneous

behavior) are offered.
A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) At night prevention and therapy / improvement medicine, such as the increment in the amount of spontaneous behavior, muscular power lowering, temperature reduction, an increment in a white blood cell count, an increment in a platelet count, reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), a pain, and morphine resistance They are the compound to which the affinity of RFRP and OT7T022 or signal transfer is changed, or its salt.
In the screening approach of this invention, it is characterized by measuring and comparing the amount of association of RFRP [as opposed to OT7T022] in (i) and (ii), cell stimulus activity, etc.
[0052]
More specifically, it is this invention,
a) The compound to which the affinity of RFRP characterized by to measure and measure the amount of association to OT7T022 of RFRP the case where RFRP which carried out the indicator is contacted to OT7T022, and at the time of contacting RFRP and the trial compound which carried out the indicator to OT7T022 which carried out the indicator, and OT7T 022, or signal transfer change, or the screening approach of the salt,
b) When RFRP which carried out the indicator is contacted to the membrane fraction of the cell containing OT7T022, or this cell, It can set, when RFRP and the trial compound which carried out the indicator are contacted to the membrane fraction of the cell containing OT7T022, or this cell. The compound to which the affinity of RFRP characterized by measuring and measuring the amount of association to this cell or this membrane fraction of RFRP which carried out the indicator, and OT7T022, or signal transfer is changed, or the screening approach of the salt,
c) When OT7T022 discovered on the cell membrane by cultivating the transformant containing DNA which carries out the code of OT7T022 for RFRP which carried out the indicator are made to contact, It can set, when OT7T022 discovered on the cell membrane by cultivating the transformant containing DNA which carries out the code of OT7T022 for RFRP and the trial compound which carried out the indicator are made to contact. The compound to which the affinity of RFRP characterized by measuring and measuring the amount of association to OT7T022 of RFRP which carried out the indicator, and OT7T022, or signal transfer is changed, or the screening approach of the salt,
[0053]
d) When the compound which activates RFRP, or its salts (for example, RFRP etc.) are contacted into the cell containing OT7T022, It can set, when the compound which activates RFRP or its salt, and a trial compound are contacted into the cell containing OT7T022. the compound to which the affinity of RFRP characterized by measuring and comparing the cell stimulus activity through OT7T022 and OT7T022 or signal transfer is changed, or the screening approach of the salt -- and

e) When OT7T022 discovered on the cell membrane by cultivating the transformant containing DNA which carries out the code of OT7T022 for the compound which activates RFRP, or its salts (for example, RFRP etc.) are made to contact, It can set, when OT7T022 discovered on the cell membrane by cultivating the transformant containing DNA which carries out the code of OT7T022 for the compound which activates RFRP or its salt, and a trial compound are made to contact. The screening approach of the compound to which the affinity of RFRP characterized by measuring and comparing the cell stimulus activity through a receptor and OT7T022 or signal transfer is changed, or its salt is offered.
By the screening approach of this invention, the compound to which the affinity of RFRP and OT7T022 is changed instead of or its salt can also be used. [RFRP] The compound to which this affinity of RFRP and OT7T022 is changed, or its salt can be obtained by enforcing the SUKUNINGU approach of this invention using RFRP.
[0054]
Concrete explanation of the screening approach of this invention is given below.
First, as OT7T022 used for the screening approach of this invention, the cell membrane fraction of the organ of the mammalian containing OT7T022 is suitable. However, since especially the organ of the Homo sapiens origin is very difficult to receive, OT7T022 of the Homo sapiens origin which carried out the large quantity manifestation, using recombinant as what is used for screening etc. are suitable. Although the approach of a publication is used [WO 00/No. 29441 or WO / 01/No. 66134] in order to manufacture OT7T022, it is desirable to carry out by discovering DNA which carries out the code of OT7T022 in a breast-feeding cell or an insect cell. Although complementary DNA is used for the DNA fragment which carries out the code of the target protein part, it is not necessarily restrained by this. For example, a gene fragment and a synthetic DNA may be used. In order to introduce into a host animal cell the DNA fragment which carries out the code of OT7T022 and to make them discover efficiently, it is desirable to build this DNA fragment into lower streams of rivers, such as the polyhedrin promotor of the nuclear polyhederosis virus (nuclear polyhedrosis virus;NPV) belonging to the baculovirus which makes an insect a host, the promotor of the SV40 origin, a promotor of a retrovirus, a metallothionein promotor, a Homo sapiens heat shock promotor, a cytomegalovirus promotor, and SRalpha promotor. The amount of a receptor and a nature inspection which were discovered can be conducted by the well-known approach in itself. For example, according to the approach of a publication, it can carry out to reference [Nambi, P. et al., THE Journal of Biological Chemistry (J.Biol.Chem.), 267 volumes, 19555-19559 pages, and 1992].
Therefore, in the screening approach of this invention, you may be OT7T022 refined as a thing containing OT7T022 according to the well-known approach in itself, and the membrane fraction of the cell which may use the cell containing OT7T022, and contains OT7T022 may be used.
[0055]
In the screening approach of this invention, when using the cell containing OT7T022, this cell may be fixed with glutaraldehyde, formalin, etc. The fixed approach can be performed according to a well-known approach in itself.
Although the host cell which discovered OT7T022 is said as a cell containing OT7T022, as this host cell, Escherichia coli, a Bacillus subtilis, yeast, an insect cell, an

animal cell, etc. are desirable.
As a cell membrane fraction, after crushing a cell, the thing of the fraction in which many cell membranes obtained by the well-known approach in itself are contained is said. Crushing by gushing a cell from a thin nozzle etc. is mentioned pressurizing as the crushing approach of a cell by the approach of crushing a cell with a Potter-Elvehjem mold homogenizer, crushing which a Waring blender and the poly TRON (product made from Kinematica) depend, crushing by the supersonic wave, an French press, etc. The fractionation method by centrifugal forces, such as a differential centrifugation method and density gradient centrifugation, is mainly used for the fractionation of a cell membrane. For example, centrifugal [of the cell crushing liquid / short-time (usually about 1 - 10 minutes)] is carried out at a low speed (500 - 3000rpm), usually carry out centrifugal [of the supernatant liquid] further for 30 minute - 2 hours at high speed (15000 - 30000rpm), and let precipitation obtained be membrane fraction. In this membrane fraction, many discovered membrane components, such as phospholipid of OT7T022 and the cell origin and membrane protein, are contained.
As for the amount of OT7T022 in the cell containing OT7T022, or membrane fraction, it is desirable that it is 103 to 108 molecule per cell, and it is suitable for it that it is 105 to 107 molecule. In addition, OT7T022 avidity per membrane fraction (specific activity) becomes high, and construction of a high sensitivity screening system is not only attained, but it can measure the sample of a large quantity with the same lot, so that there are many amounts of manifestations.
[0056]
In order to carry out above-mentioned a-c which screen the compound to which the affinity of RFRP and OT7T022 or signal transfer is changed, or its salt, RFRP which carried out the indicator to OT7T022 suitable fraction, for example is required. Recombinant OT7T022 fraction which has activity equivalent to OT7T022 fraction of a natural mold or it as OT7T022 fraction is desirable. Here, equivalent ligand avidity, a signal signal transduction operation, etc. are indicated to be equivalent activity.
As RFRP which carried out the indicator, RFRP which carried out the indicator, the RFRP analog compound which carried out the indicator are used. For example, RFRP by which the indicator was carried out by [3H], [125I], [14C], [35S], etc. is used.
In order to specifically screen the compound to which the affinity of RFRP and OT7T022 or signal transfer is changed, OT7T022 preparation is prepared by suspending the membrane fraction of the cell which contains OT7T022 first, or a cell in the buffer suitable for screening. Any are sufficient as long as it is the buffer which does not check association with RFRP(s), such as a phosphoric-acid buffer of pH 4-10 (desirably pH 6-8), and a tris-hydrochloric-acid buffer, and OT7T022 in a buffer. Moreover, surface active agents, such as CHAPS, Tween-80TM (Kao-atlas company), digitonin, and a deoxycholate, can also be added to a buffer in order to reduce nonspecific association. Furthermore, protease inhibitors, such as PMSF, leupeptin, E-64 (made in a peptide lab), and pepstatin, can also be added in order to suppress the decomposition of OT7T022 or RFRP by the protease. RFRP in which the constant rate (5000-500000cpm) carried out the indicator to this 0.01-10ml receptor solution is added, and the trial compound of 10-4M-10-10M is made to live together simultaneously. In order to know the amount (NSB) of nonspecific association, the reaction tube which added RFRP of the non-indicator of an overlarge is also prepared.

About 0-50 degrees C, a reaction is about 4-37 degrees C, and is performed desirably for about 30 minutes to 3 hours for about 20 minutes to 24 hours. It filters through a glass fiber filter paper etc. after a reaction, and after washing by this buffer of optimum dose, the radioactivity which remains in a glass fiber filter paper is measured at a liquid scintillation counter or gamma-counter. When the count (B0-NSB) which subtracted the amount (NSB) of nonspecific association from the count (B0) in case there is no matter which rivals is made into 100%, the amount (B-NSB) of specific bindings can choose the trial compound which becomes 50% or less as candidate matter with antagonistic inhibition capacity.

[0057]

In order to enforce the above-mentioned approach of d-e which screens the compound to which the affinity of RFRP and OT7T022 or signal transfer is changed, or its salt, the cell stimulus activity through OT7T022 can be measured using a well-known approach or the commercial kit for measurement.

Specifically, the cell containing OT7T022 is first cultivated on a multi-well plate etc. After exchanging for the suitable buffer which does not show toxicity to a fresh culture medium or a fresh cell beforehand in screening, adding a trial compound etc. and carrying out fixed time amount incubation, according to each approach, the quantum of the product which collected and generated the cell for an extract or digestive liquor is carried out. When assay with the dialytic ferment which a cell contains is difficult for the generation of matter (for example, arachidonic acid etc.) made into the index of cell stimulus activity, the inhibitor to this dialytic ferment may be added and assay may be performed. Moreover, about activity, such as cAMP production control, it is detectable as production depressant action to the cell which increased the amount of fundamental production of a cell by forskolin etc.

In order to screen by measuring cell stimulus activity, the cell which discovered OT7T022 [suitable] is required. As a cell which discovered OT7T022, the cell strain which has OT7T022 of a natural mold, the cell strain which discovered above recombinant OT7T022 are desirable.

The same thing as the above is used as a trial compound.

Moreover, the compound designed so that it might combine with a ligand joint pocket as a trial compound based on the location of the atomic coordinate of the active site of OT7T022 and a ligand joint pocket is used preferably. Measurement of the location of the atomic coordinate of the active site of OT7T022 and a ligand joint pocket can be performed using the approach according to a well-known approach or well-known it.

[0058]

The compound to which the affinity of RFRP and OT7T022 or signal transfer is changed, or the kit for screening of the salt contains RFRP, the cell containing OT7T022, or its cell membrane fraction.

The following are mentioned as an example of the kit for screening of this invention.

1. Reagent for Screening

a) The buffer solution for measurement, and the buffer solution for washing

What added 0.05% of bovine serum albumin (sigma company make) to Hanks' Balanced Salt Solution (Gibco make).

or it carries out filtration sterilization with the filter of 0.45 micrometers of apertures and saves at 4 degrees C -- or business -- the time -- you may prepare .

b) OT7T022 preparation
What carried out the passage of the CHO cell which made OT7T022 discover to 12 hole plate in 5x105 pieces / hole, and cultivated it for two days by 37 degrees C, 5%CO2, and 95%air.
c) Indicator RFRP
RFRP which carried out the indicator by [3H] of marketing, [125I], [14C], [35S], etc. the thing of the condition of a water solution -- 4 degrees C or -20 degrees C -- saving -- business -- it sometimes dilutes with the buffer solution for measurement at 1microM.
d) RFRP standard solution
RFRP is dissolved so that it may be set to 1mM by PBS which contains bovine serum albumin (sigma company make) 0.1%, and it saves at -20 degrees C.
[0059]
2. Measuring Method
a) After 1ml of buffer solutions for measurement washes twice the OT7T 022 manifestation CHO cell cultivated on the plate for 12 hole tissue culture, add the buffer solution for measurement of 490microl to each hole.
b) 5microl Add Indicator RFRP and make it react at a room temperature for 1 hour, after 5microl Adding the trial compound solution of 10-3-10-10M. 5microl In order to know the amount of nonspecific association, add RFRP of 10-3M instead of the trial compound.
c) Remove reaction mixture and the 1ml buffer solution for washing washes 3 times. The indicator RFRP combined with the cell is dissolved by 0.2N NaOH-1%SDS, and it mixes with 4ml liquid-scintillator A (Wako Pure Chem make).
d) Measure radioactivity using a liquid scintillation counter (made in Beckmann), and calculate Percent Maximum Binding (PMB) by the following formula.
PMB=[(B-NSB)/(B0-NSB)] x100
PMB:Percent Maximum Binding
B : the value when adding a specimen
NSB:Non-specific Binding (the amount of nonspecific association)
B0 : The amount of the maximum association
[0060]
As a compound obtained using the screening approach of this invention, or the kit for screening, a peptide, protein, a nonpeptidic compound, a synthetic compound, a fermentation product, a cell extract, a vegetable extract, an animal tissue extract, plasma, etc. may be mentioned, and these compounds may be new compounds and may be well-known compounds.
As a salt of the compound obtained by the above-mentioned screening approach, the above mentioned salt of RFRP and the same salt are used.
The compound obtained using the screening approach of this invention, or the kit for screening, or its salt They are the compound which has the operation which changes the affinity of RFRP and OT7T022, or signal transfer, or its salt. Specifically the compound which has cell stimulus activity through (b) OT7T022, or its salt (being the so-called --) OT7T022 agonist, the compound which does not have (b) this cell stimulus activity, or its salt (being the so-called --) They are OT7T022 antagonist, the compound which reinforces the bonding strength of RFRP (Ha) and OT7T022, its salt, the compound which decreases the bonding strength of (d) RFRP and OT7T022, or its

salt.
The concrete assessment approach of whether it is OT7T022 agonist or to be an antagonist should just follow the following (i) and (ii).
(i) For example, binding assay shown by said screening approach of a-c is performed, and after obtaining the compound to which the affinity of RFRP and OT7T022 is changed (association is checked especially), or its salt, it measures whether it has the cell stimulus activity through OT7T022 which this compound or its salt described above. The compound which has cell stimulus activity, or its salt is OT7T022 agonist, and the compound which does not have this activity, or its salt is OT7T022 antagonist.

(ii) (a) trial compound is contacted into the cell containing OT7T022, and the cell stimulus activity through the above-mentioned OT7T022 is measured. The compound which has cell stimulus activity, or its salt is OT7T022 agonist.
(b) Measure and compare the cell stimulus activity through OT7T022 the case where the compounds (for example, RFRP etc.) which activate OT7T022 are contacted into the cell containing OT7T022, and at the time of contacting the compound and trial compound which activate OT7T022 into the cell containing OT7T022. The compound which may decrease cell stimulus activity with the compound which activates OT7T022, or its salt is OT7T022 antagonist.
the operation as the bioactive which RFRP has with OT7T022 same agonist -- having -- **** -- safe -- low -- it is useful as a toxic remedy.
the insurance for controlling the bioactive of RFRP, since OT7T022 antagonist can control the bioactive which RFRP has -- low -- it is useful as a toxic remedy.
since the compound which reinforces the bonding strength of RFRP and OT7T022, or its salt can reinforce the bioactive which RFRP has -- safe -- low -- it is useful as a toxic remedy.
the insurance for controlling the bioactive of RFRP, since the compound which decreases the bonding strength of RFRP and OT7T022, or its salt can decrease the bioactive which RFRP has -- low -- it is useful as a toxic remedy.
[0061]
The compound which specifically reinforces the bonding strength of OT7T022 agonist and RFRP which are obtained using the screening approach of this invention, or the kit for screening, and OT7T022, or its salt For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) The increment in the amount of spontaneous behavior, muscular power lowering, etc. are especially useful at night as a prevention and therapy / improvement agent to an increment or muscular power lowering of the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior).
The compound which, on the other hand, decreases the bonding strength of OT7T022 antagonist and RFRP which are obtained using the screening approach of this invention, or the kit for screening, and OT7T022, or its salt For example, it is useful as

the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count or prevention and therapy / improvement agent to reduction of the amount of spontaneous behavior (especially night the amount of spontaneous behavior), a painkiller, the analgesic action accelerator of morphine, a morphine resistance evasion agent, a morphine dependency evasion agent, etc.

When using the compound obtained using the screening approach of this invention, or the kit for screening, or its salt as the above-mentioned remedy constituent, it can pharmaceutical-preparation-ize according to a stock-in-trade. It can manufacture like prevention and therapy / improvement agent which specifically contains the above-mentioned RFRP.

The pharmaceutical preparation obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to Homo sapiens or mammalians (for example, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example.

Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in a nociception failure patient, about 0.1-100mg of about 1.0-50mg of doses of this compound or its salt is about 1.0-20mg more preferably about OT7T022 agonist per day (as weight of 60kg).

Although a dose changes with the object organ for administration, a symptom, medication methods, etc. once [the] when prescribing a medicine for the patient parenterally For example, in the form of injections, it usually sets to a nociception failure patient, for example (as weight of 60kg). It is convenient per day to prescribe more preferably about about 0.01-30mg about about 0.1-20mg about about 0.1-10mg for the patient for OT7T022 agonist by the intravenous injection. The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

[0062]

(6) The remedy containing the compound to which the amount of OT7T022 in a cell membrane is changed, or its salt

Since the antibody to OT7T022 can recognize OT7T022 specifically, it can be used for screening of the compound to which the amount of OT7T022 in a cell membrane is changed, or its salt.

namely, this invention -- for example

(i) The compound to which the amount of OT7T022 in a cell membrane by carrying out the quantum of the OT7T022 which isolate a cell membrane fraction and are contained in a cell membrane fraction after destroying an organization or a cell isolated from a blood of a nonhuman mammal, the organ of b specification, and c organ is changed, or the screening approach of the salt,

(ii) The compound to which the amount of OT7T022 in a cell membrane by carrying out the quantum of the OT7T022 which isolate a cell membrane fraction and are contained in a cell membrane fraction after destroying the transformant which discovers OT7T022 is changed, or the screening approach of the salt,

(iii) After using as an intercept an organization or a cell isolated from a blood of a nonhuman mammal, the organ of b specification, and c organ, the screening approach of the compound to which the amount of OT7T022 in a cell membrane by checking this protein on a cell membrane is changed, or its salt is offered by quantifying the

dyeing degree of this receptor protein in a cell cortex by using an immunity staining technique.
(iv) After using as an intercept the transformant which discovers OT7T022, the screening approach of the compound to which the amount of OT7T022 in a cell membrane by checking this protein on a cell membrane is changed, or its salt is offered by quantifying the dyeing degree of this receptor protein in a cell cortex by using an immunity staining technique.
[0063]
The quantum of OT7T022 contained in a cell membrane fraction is specifically performed as follows.
(i) As opposed to normal or disease model nonhuman mammals (for example, more specifically [a mouse, Latt, a rabbit, a sheep, Buta a cow, a cat, a dog, an ape etc.] immune disorder Latt, a mouse, a ** rabbit, etc.) Drugs (for example, immunomodulator etc.) or physical stress (For example, flooding stress, an electroshock, light and darkness, low temperature, etc.) etc. -- after giving and carrying out fixed time amount progress, the organization which isolated from blood, specific organs (for example, a brain, liver, the kidney, etc.), or an organ, or a cell is obtained. An obtained organ, an organization, or a cell is suspended in the suitable buffer solutions (for example, the tris hydrochloric-acid buffer solution, a phosphate buffer solution, the HEPESU buffer solution, etc.) etc., for example, an organ, an organization, or a cell is destroyed, and a cell membrane fraction is further obtained using technique, such as centrifugal separation, and filtration, column fractionation, using surfactants (for example, triton X100TM, Tween 20TM, etc.) etc.
As a cell membrane fraction, after crushing a cell, the thing of the fraction in which many cell membranes obtained by the well-known approach in itself are contained is said. Crushing by gushing a cell from a thin nozzle etc. is mentioned pressurizing as the crushing approach of a cell by crushing by the approach and Waring blender which crush a cell with a Potter-Elvehjem mold homogenizer, or the poly TRON (product made from Kinematica), crushing by the supersonic wave, an French press, etc. The fractionation method by centrifugal forces, such as a differential centrifugation method and density gradient centrifugation, is mainly used for the fractionation of a cell membrane. For example, centrifugal [of the cell crushing liquid / short-time (usually about 1 minute - 10 minutes)] is carried out at a low speed (500 - 3000rpm), usually carry out centrifugal [of the supernatant liquid] further for 30 minute - 2 hours at high speed (15000 - 30000rpm), and let precipitation obtained be membrane fraction. In this membrane fraction, many discovered membrane components, such as phospholipid of OT7T022 and the cell origin and membrane protein, are contained.
The quantum of the OT7T022 contained in a cell membrane fraction can be carried out by sandwiches immunoassay, western blot analysis, etc. which used the antibody of this invention.
the approach of the above [this sandwiches immunoassay] -- the same -- carrying out -- it can carry out -- western blotting -- the very thing -- a well-known means can perform.
(ii) The transformant which discovers OT7T022 can be produced according to the above-mentioned approach, and the quantum of the OT7T022 contained in a cell membrane fraction can be carried out.
[0064]

Screening of the compound to which the amount of OT7T022 in a cell membrane is changed, or its salt,
(i) Before fixed time amount which gives drugs or physical stress to normal or a disease model nonhuman mammal (30 quotas - 24 hours ago) It is 1 hour before - 6 hours ago or after fixed time amount (after 30 minutes - three days after) more preferably 30 quotas - 12 hours ago. More preferably 1 hour after - two days after 1 hour after - 24 hours after, Or drugs or physical stress, and coincidence can be medicated with a trial compound, and it can carry out by carrying out the quantum of the amount of OT7T022 in a cell membrane after after [administration] fixed time amount progress (1 hour after - two days after [After 30 minutes - three days after preferably] more preferably 1 hour after - 24 hours after),
(ii) In case a transformant is cultivated according to a conventional method, a trial compound can be mixed in a culture medium, and it can carry out by carrying out the quantum of the amount of RFRP in a cell membrane after fixed time amount culture (one day after - three days after [One day after - seven days after preferably] more preferably two days after - three days after).
The check of OT7T022 contained in a cell membrane fraction is specifically performed as follows.
As opposed to normal or disease model nonhuman mammals (for example, more specifically [a mouse, Latt, a rabbit, a sheep, Buta, a cow a cat, a dog, an ape, etc.] an immune disorder model rat, a mouse, a rabbit, etc.) (iii) Drugs (for example, immunomodulator etc.) or physical stress (For example, flooding stress, an electroshock, light and darkness, low temperature, etc.) etc. -- after giving and carrying out fixed time amount progress, the organization which isolated from blood, specific organs (for example, a brain, liver, the kidney, etc.), or an organ, or a cell is obtained. An obtained organ, an organization, or a cell is used as an organization intercept according to a conventional method, and immunity dyeing is performed using the antibody of this invention. By quantifying the dyeing degree of this receptor protein in a cell cortex, the amount of OT7T022 in a cell membrane can be checked quantitatively or qualitatively by checking this protein on a cell membrane.
(iv) It can also check by taking the same means using the transformant which discovers OT7T022.
The same thing as the above is used as a trial compound.
[0065]
The compound obtained using the screening approach of this invention is a compound which has the operation which changes the amount of OT7T022 in a cell membrane, and is the compound which specifically decreases this cell stimulus activity by decreasing the amount of OT7T022 in the compound and the (b) cell membrane which reinforce the cell stimulus activity which minds OT7T022 by making the amount of OT7T022 in a (b) cell membrane increase.
As a salt of the compound obtained by the above-mentioned screening approach, the above mentioned salt of RFRP and the same salt are used.
The compound which reinforces cell stimulus activity by making the amount of OT7T022 in a cell membrane increase, or its salt For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function

failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) Especially the increment in the amount of spontaneous behavior, muscular power lowering, etc. at night The myonosus, adrenal insufficiency, It is useful as a **** [which it is safe and is low toxicity] and therapy / improvement agent to an increment or muscular power lowering of a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior).

The compound which decreases cell stimulus activity by decreasing the amount of OT7T022 in a cell membrane, or its salt For example, the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially) It is useful at night as **** [which it is safe and is low toxicity] and therapy / improvement agent to reduction of the amount of spontaneous behavior, a painkiller, the analgesic action accelerator of morphine, a morphine resistance evasion agent, a morphine dependency evasion agent, etc.

When using the compound obtained using the screening approach of this invention, or its salt as a remedy constituent, it can pharmaceutical-preparation-ize according to a stock-in-trade. It can manufacture like prevention and therapy / improvement agent which specifically contains the above-mentioned RFRP.

The pharmaceutical preparation obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to Homo sapiens or mammalians (for example, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example.

Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally, about 0.1-100mg per day of about 1.0-50mg of doses of this compound or its salt is about 1.0-20mg more preferably about the compound to which the amount of OT7T022 in a cell membrane is made to increase in a nociception failure patient, or its salt (as weight of 60kg). Although a dose changes with the object organ for administration, a symptom, medication methods, etc. once [the] when prescribing a medicine for the patient parenterally For example, in the form of injections, it usually sets to a nociception failure patient, for example (as weight of 60kg). It is convenient to prescribe more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient for the compound to which the amount of OT7T022 in a cell membrane is made to increase, or its salt by the intravenous injection. The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

[0066]

(7) The remedy which comes to contain RFRP or the antibody to OT7T022

An antibody (especially neutralizing antibody) can inactivate the signal transfer in which RFRP or OT7T022 participate, for example, the cell stimulus activity through OT7T022, to RFRP or OT7T022.

Therefore, RFRP or the antibody to OT7T022 can be used as the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count or prevention and therapy / improvement agent to reduction of the amount of spontaneous behavior (especially night the amount of

spontaneous behavior), a painkiller, the analgesic action accelerator of morphine, a morphine resistance evasion agent, a morphine dependency evasion agent, etc.
The above-mentioned prevention and therapy / improvement agent can be manufactured like the remedy containing the above mentioned RFRP, and can be used.
[0067]
(8) The remedy which comes to contain an antisense DNA or siRNA
The antisense DNA to DNA which carries out the code of the antisense DNA to DNA which carries out the code of the RFRP, or OT7T022 (It is hereafter written as an antisense DNA) Or siRNA of this invention For example, the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially) It can use at night as prevention and therapy / improvement agent to reduction of the amount of spontaneous behavior, a painkiller, the analgesic action accelerator of morphine, a morphine resistance evasion agent, a morphine dependency evasion agent, etc.
For example, when using this antisense DNA or siRNA, after inserting this antisense DNA or siRNA in suitable independent or vectors, such as a retrovirus vector, an adenovirus vector, and an adenovirus-associated virus vector, it can carry out according to a stock-in-trade. This antisense DNA or siRNA remains as it is, or for acceleration of intake, is pharmaceutical-preparation-ized with support accepted physiologically, such as an adjuvant, and can be prescribed for the patient with a catheter like a gene gun or a hydro gel catheter.
Furthermore, this antisense DNA can also be used as an oligonucleotide probe for a diagnosis for investigating existence of DNA which carries out the code of RFRP in an organization or a cell or OT7T022, and its manifestation situation.
[0068]
(9) OT7T 022 knockout animal
[OT7T 022 gene-expression inactive mammalian embryonic stem cell]
With the mammalian embryonic stem cell by which OT7T022 gene was inactivated By adding variation to OT7T022 gene which a mammalian embryonic stem cell has artificially By making the activity of OT7T022 in which control gene expression ability or this gene is carrying out the code lose substantially A gene says the embryonic stem cell of the inactivated mammalian (the knockout gene of this invention may be called hereafter) which does not have the manifestation ability of OT7T022 substantially.
Array number:32 or an array number which carries out the code of the partial protein of mouse OT7T022 which specifically consists of an amino acid sequence expressed with array number:27 as mouse OT7T022 gene although DNA which carries out the code of the above mentioned OT7T022 as OT7T022 gene is used: The gene (genomic DNA) which consists of a base sequence expressed with 28 is used.
The array number which carries out the code of the OT7T022 which consist of an amino acid sequence expressed with array number:11 as Latt OT7T022 gene: The gene containing the base sequence expressed with 12 etc. is used.
As mammalian used as the ingredient of an embryonic stem cell, Homo sapiens, a cow, Buta, a sheep, a goat, a rabbit, a dog, a cat, a guinea pig, a hamster, a mouse, Latt, etc. are used among this description, for example.

Moreover, among this description, although what kind of animal is sufficient as long as it is animals other than the Homo sapiens who has OT7T022 gene as a nonhuman animal, a nonhuman mammal is desirable. As a nonhuman mammal, a cow, Buta, a sheep, a goat, a rabbit, a dog, a cat, a guinea pig, a hamster, a mouse, Latt, etc. are used, for example. The GETSU gear-tooth animal with propagation a field to the ontogeny and biocycle of production of a model-animal-of-pathosis system are comparatively short, and easy also in a nonhuman mammal, a division mouse (for example, as a pure line strain) They are B6C3F1 line, one BDF, B6D2F1 line, a BALB/c system, an ICR system, etc. as hybridization systems, such as C57BL / six lines, and two DBA(s), (preferably especially). As a pure line strain, C57BL / six etc. lines of especially Latt (for example, a Wistar system, SD system, etc.), such as one BDF or an ICR system, etc. are desirable as a hybridization system.

[0069]

As an approach of adding variation to OT7T022 gene artificially, insertion or the permutation of this a part of gene sequence, all deletion, or other genes is raised by the gene engineering-technique, for example. The knockout gene of this invention is producible by shifting the reading frame of a codon or destroying the function of a promotor or an exon by these variation.

Mammalian by which OT7T022 gene was inactivated (preferably) As an example of a nonhuman mammal embryonic stem cell (it is hereafter written as an OT7T 022 gene inactivation embryonic stem cell or a knockout embryonic stem cell) For example, a drug resistance gene (for example, preferably a neomycin resistance gene, a hygromycin tolerance gene, or a ZEOSHIN resistance gene) Reporter genes, such as a neomycin resistance gene (For example, it lacZ(s) and (Escherichia coli beta-galactosidase gene) cat(s) (chloramphenicol acetyltransferase gene).) GUS (beta-glucuronidase gene), a luciferase gene, an aequorin gene, A TAUMARIN gene, a GFP (Green Fluorescent Protein) gene, etc. preferably lacZ etc. — etc. — whether the function of the exon of OT7T022 gene is destroyed by inserting Or by inserting the DNA arrays (for example, polyA addition signal etc.) which make the intron part between exons end the imprint of a gene, and carrying out by the ability not compounding perfect mRNA The DNA vector (it is hereafter written as a targeting vector) which has the DNA array built so that a gene might be destroyed as a result is produced. When inserting a reporter gene and destroying the function of an exon, as for this reporter gene, it is desirable to insert so that it may be discovered under OT7T022 promotor's control.

It is used as a marker which selects whether the above "a drug resistance gene" showed the gene which participates in the drug tolerance of an antibiotic etc., and the gene introduced was discovered in the cell.

The above "a reporter gene" shows the thing of the gene cluster which becomes the index of gene expression, and the structural gene of the enzyme which carries out the catalyst of a luminous reaction or the color reaction is usually used in many cases. Moreover, **1 A thing, **2 without a genetic background A thing, **3 with the approach of the high sensitivity which can perform gene expression quantitatively What has the few effect on a transformed cell, **4 That the localization of a manifestation part is indicated to be is used preferably (a vegetable cell technology, the 2nd volume, the 721st page, 1990). Moreover, although the above-mentioned "drug resistance gene" etc. is used for the same object, a "reporter gene" can

investigate in which organization it was [when] discovered the gene only introduced was not only discovered in the cell, but, and can investigate the amount of manifestations to accuracy quantitatively.
Furthermore, it can analyze by the PCR method which made the primer the DNA array on the Southern hybridization analysis which introduced the targeting vector into the chromosome of this animal for example, by the homologous rearranging method, and used the DNA array of an OT7T 022 gene top or its near as the probe about the obtained embryonic stem cell, or a targeting vector, and the DNA array of near fields other than the OT7T022 gene used for targeting vector production, and can obtain by sorting out the knockout embryonic stem cell of this invention.
as the above-mentioned targeting vector -- the plasmid (an example --) of for example, the Escherichia coli origin the plasmid (an example --) of the Bacillus-subtilis origins, such as pBR322, pBR325, pUC12, and pUC13 the plasmid (an example --) of the yeast origins, such as pUB110, pTB5, and pC194 Bacteriophages, such as lambda phage, such as pSH19 and pSH15, Animal viruses, such as retroviruses, such as a Moloney leukemia virus, a vaccinia virus or an adenovirus vector, a baculovirus, a bovine papilloma virus, a virus from a Herpes virus group, or an Epstein-Barr virus, etc. are used.
[0070]
Moreover, what could use the already established above things, for example as an embryonic stem cell of the origin which makes OT7T022 gene inactivate by the homologous rearranging method etc., and was newly established according to the approach of well-known Evans and Kaufman may be used. For example, in the case of the embryonic stem cell of a mouse, 129 embryonic stem cells are used for current and a general target, but For the object of a genetic background acquiring a clear embryonic stem cell immunologically by the pure line strain replaced with this, since the immunological background has not clarified For example, what was established using C57BL / six-line mouse, or DBA / two one crossbreed BDF mice (C57BL / six lines, DBA / two F1) can be used good. the advantage that an one BDF mouse has many egg gathering, and it is in [an egg operating it] -- in addition, since it has C57BL / six-line mouse in a genetic background, the embryonic stem cell obtained using this can be advantageously used at the point which can return the genetic background to C57BL / six lines by carrying out a back cross to C57BL / six-line mouse, when a symptoms model mouse is created.
Moreover, although a day [of carrier Seigo / 3.5th] blastocyst is generally used when establishing an embryonic stem cell, the eggs of 8 cell term germ (8 cell term germ at the 2.5th day time of carrier Seigo is desirable) can be gathered in addition to this, and many early embryos can be efficiently acquired by cultivating and using to a blastocyst.
[0071]
Moreover, the karyotype analysis which used the G-banding method etc. can perform the second selection. Although 100% of the normal number of the chromosome number of the embryonic stem cell obtained is desirable, when a relation top, such as physical actuation in the case of establishment, is difficult, after knocking out the gene of an embryonic stem cell, it is desirable to carry out cloning to a normal cell (for example, cell whose chromosome number is 2n=40 with a mouse) again.
Thus, although it is usually very good, since the obtained embryonic stem cell stock

tends to lose the regenerative capacity which can carry out ontogeny, it needs to carry out subculture carefully. [of the fecundity] For example, it is the inside of a carbon-dioxide-gas incubator (preferably) under LIF (1-10000U/ml) existence on a suitable feeder cell like STO fibrocyte. It cultivates by the approach of cultivating at about 37 degrees C 5% with carbon dioxide gas, 95% air or 5% oxygen, 5% carbon dioxide gas, and 90% air. At the time of a passage For example, it single-cell-izes by the trypsin / EDTA solution (usually 0.001 - 0.5% trypsin / 0.1 - 5mM EDTA, preferably about 0.1% trypsin / 1mM EDTA) processing, and the approach of carrying out seeding on the newly prepared feeder cell etc. is taken. Although such a passage is usually performed day by day [1 - 3], when a cell is observed on this occasion and a cell unusual in gestalt is able to see, to abandon that cultured cell is desired.
By carrying out suspended cell culture until it carries out monolayer culture of it according to suitable conditions until an embryonic stem cell results in high density, or it forms a cell cluster It is possible to make it specialize in the cell of various types, such as a top-of-the-head muscle, a visceral muscle, and a myocardium. [M.J.Evans and M.H.Kaufman, the 292nd volume (Nature) of Nature, 154 pages and 1981;G.R.Martin The 78th volume (Proc.Natl.Acad.Sci.U.S.A.) of Proceedings of National Academy of Science U.S.A., 7634 pages and 1981;T.C.Doetschman ** -- Journal OBU embryo logy - and - experimental mol follow G, The 87th volume, 27 pages, 1985], and the OT7T 022 gene-expression insufficient cell that the embryonic stem cell of this invention is made to specialize, and is obtained are useful in the cell biological examination of OT7T022 in in vitro.
Moreover, the culture medium for freezing suitable when saving an embryonic stem cell (for example, 10%DMSO, the Dulbecco's modified Eagle's medium (DMEM) which contains fetal calf serum 10% are used, and it is [about] -[Cryopreservation is carried out below 80 degrees C.])
[0072]
The OT7T 022 gene-expression insufficient nonhuman animal (a gene expression insufficient nonhuman animal may be called hereafter) of this invention is a nonhuman animal which it was created in gene engineering using the cell of the mammalian embryonic stem cell origin by which the OT7T022 aforementioned gene was inactivated, for example, was introduced into the reproductive cell and the somatic cell in inactivation OT7T022 gene sequence in early stages of embryogenesis.
The same thing as the above is used as this nonhuman animal.
In order to make OT7T022 gene knock out The aforementioned targeting vector An approach well-known to a nonhuman animal embryonic stem cell or a nonhuman animal ootid for example, the electroporation method and a microinjection method -- a calcium phosphate method, the RIPOFE cushion method, a condensation method, and party Kurgan -- law, the DEAE-dextran method, etc. -- introducing (as a desirable introducing method) A microinjection method etc. is raised when introducing into the electroporation method and an ootid, in introducing into an embryonic stem cell.
Homologous recombination can perform OT7T022 gene sequence by which the targeting vector was inactivated by changing for OT7T022 gene on the chromosome of a nonhuman animal embryonic stem cell or a nonhuman animal ootid. The cell by which OT7T022 gene was knocked out can be judged in the analysis by the PCR method which made the primer the Southern hybridization analysis which used the DNA array of an OT7T 022 gene top or its near as the probe or the DNA array on a targeting

vector, and the DNA array of near fields other than the OT7T022 gene of the mouse origin used for the targeting vector.
When a nonhuman animal embryonic stem cell is used, cloning of the cell strain by which OT7T022 gene was inactivated is carried out by homologous recombination. The cell is injected into the nonhuman animal germ or blastocyst of a suitable stage [in early stages of embryogenesis], for example, 8 cells, term (the pouring-in method). Or the chimera germ produced by what the embryonic stem cell lump with which OT7T022 gene was inactivated is inserted for by 8 cell term germ of two pieces (the set chimera method) is transplanted to the uterus of this nonhuman animal that carried out pseudopregnancy.
The created animal is a chimera animal which consists of both a cell with OT7T022 normal locus, and a cell with OT7T022 locus which varied artificially.
When it has OT7T022 locus to which a part of reproductive cell of this chimera animal varied, it is obtained from the population obtained by crossing such a chimera individual and a normal individual by sorting out the individual which consisted of cells with OT7T022 locus to which all organizations added variation artificially by the judgment of for example, a coat color etc. Thus, the obtained individual is an OT7T 022 hetero manifestation insufficient individual, can cross an OT7T 022 hetero manifestation insufficient individual comrade, and can usually obtain an OT7T 022 gay manifestation insufficient individual from those offspring.
When using an ootid, by pouring in a gene solution by the microinjection method into an ootid nucleus, the transgenic nonhuman animal which introduced the targeting vector in the chromosome can be obtained, and it is obtained by comparing these transgenic nonhuman animals by choosing what has variation in OT7T022 locus by homologous recombination.
An OT7T 022 gene-expression insufficient nonhuman animal can be distinguished from the normal animal by measuring the amount of mRNA(s) of this animal using a well-known approach, and measuring the amount of manifestations indirectly.
[0073]
Thus, the animal individual obtained by mating can also check that this gene is knocked out, and the individual by which OT7T022 gene is knocked out can perform a breeding passage for it in the usual breeding environment.
Furthermore, according to a conventional method, it can carry out also about acquisition and maintenance of a germ cell line. That is, the homozygote animal which has this inactivation gene sequence in both homologues is acquirable by crossing the animal of the sex which holds this inactivation gene sequence. The obtained homozygote animal can be efficiently obtained by breeding in the condition that it becomes the normal individual 1 and homozygote plurality, to a mother animal. By crossing the sex of a heterozygote animal, the propagation passage of the homozygote which has this inactivation gene sequence, and the heterozygote animal can be carried out. Thus, the descendant of an animal who has this acquired inactivation gene sequence is also contained in the OT7T 022 gene-expression insufficient nonhuman animal of this invention.
The OT7T 022 gene-expression insufficient nonhuman animal (OT7T 022 gay deficit nonhuman animal, preferably [Especially] OT7T 022 gay deficit mouse) of this invention has the following properties.
(1) Compared with a wild type animal, thymic weight is increasing after mature age.

(2) Compared with a wild type animal, a tremor or a convulsion may be shown in the gait abnormality pan characterized [main] by the opisthoporeia.
(3) Compared with a wild type animal, reactant lowering is seen to a noxious stimulus (an example, heat noxious stimulus).
(4) There is much offensive action compared with a wild type animal.
(5) Compared with a wild type animal, lowering of kidney absolute weight or thymus gland absolute weight is seen.
(6) Compared with a wild type animal, reduction of a white blood cell count or a platelet count is seen.
(7) Muscular power is declining compared with a wild type animal.
[0074]
Thus, the mammalian embryonic stem cell by which OT7T022 gene was inactivated is dramatically useful when creating an OT7T 022 gene-expression insufficient nonhuman animal. Moreover, the symptoms model animal produced with the drugs induction or the stress load to an OT7T 022 gene-expression insufficient nonhuman animal and this animal, Rather than it is generated by mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals A good symptoms model animal, By mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals The symptoms model animal produced with the drugs induction or the stress load to the symptoms model animal to produce, and the bone marrow transplantation animal using an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals, Or the cell originating in those organization or them Are based on the deletion of the disease resulting from the deficit of OT7T022, for example, the various bioactive which may be guided by OT7T022. the disease (for example, a nociception failure --) resulting from inactivation of the bioactive of OT7T022 An eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, Adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, depression, uneasy **, A reproductive function failure, obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, The increment in white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), Since it can become better models, such as an increment in the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power lowering, especially, muscular power lowering etc. It is useful to cause investigation of these diseases and examination of a cure. They are [Linton to which the model mouse using the bone marrow transplantation which carried out the ** office to the deficit or lifting of the gene expression only by the side of a blood cell is also mentioned as other symptoms model animals here, for example, M.F., et al., and Science 267. : 1034-1037 (1995)]. A bone marrow transplantation mouse is that the ** office of the change of a gene function is carried out, and hides possibility of becoming the more suitable symptoms model animal. For example, the symptoms model animal obtained from the OT7T 022 gene-expression insufficient nonhuman animal described above is made into a donor animal. The mouse transplanted to other recipient animals which extracted the bone marrow and destroyed bone marrow by

radiation irradiation beforehand, Or the bone marrow is extracted by making other symptoms model animals into a donor animal, and the bone marrow transplantation mouse which transplanted the symptoms model animal obtained from the OT7T 022 gene-expression insufficient nonhuman animal which destroyed bone marrow by radiation irradiation beforehand as a recipient animal is contained.
Thus, the symptoms model animal produced with the drugs induction or the stress load to the OT7T 022 gene-expression insufficient nonhuman animal of this invention, and this animal, The symptoms model animal produced by mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals, The symptoms model animal produced with the drugs induction or the stress load to the symptoms model animal produced by mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals, The symptoms model animal obtained by carrying out a bone marrow transplantation using the symptoms model animal obtained from the OT7T 022 gene-expression insufficient nonhuman animal, and other symptoms model animals, Or the cell originating in those organization or they can be used for screening of prevention and therapy / improvement medicine of this disease. Here, or it measures specific activity, using homogenates, such as liver and the kidney, as an example of the cell originating in the above-mentioned organization or it, it can use for screening by measuring the activity and the amount of production of a specific product using a peritoneal macrophage.
[0075]
[The screening approach A of this invention]
It is characterized by using the cell originating in the OT7T 022 gene-expression insufficient nonhuman animal of this invention, its organization, or them for this invention. A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, An increment or muscular power lowering of a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, The increment in a nociception failure, the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior or the screening approach of prevention and therapy / improvement medicine muscular power lowering is offered especially.
The OT7T 022 gene-expression insufficient nonhuman animal used in the screening approach of this invention, The symptoms model animal produced with drugs induction or the stress load of this animal, The symptoms model animal produced by mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals, The symptoms model animal produced with the drugs induction or the stress load to the symptoms model animal produced by mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals, The same thing as the above is mentioned as a cell originating in the symptoms model animals obtained by carrying out a bone marrow transplantation using the symptoms model animal obtained from the OT7T 022 gene-expression insufficient nonhuman animal, and other symptoms model animals, those organizations, or them.
The same thing as the above is used as a trial compound.

The symptoms model animal specifically produced with drugs induction or the stress load of the OT7T 022 gene-expression insufficient nonhuman animal of this invention, and this animal, The symptoms model animal produced by mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals, By mating with an OT7T 022 gene-expression insufficient nonhuman animal and other symptoms model animals The symptoms model animal obtained by carrying out a bone marrow transplantation using the symptoms model animal obtained from the symptoms model animal and OT7T 022 gene-expression insufficient nonhuman animal which are produced with the drugs induction or the stress load to the symptoms model animal to produce, and other symptoms model animals (hereafter) An OT7T 022 gene-expression insufficient nonhuman animal etc. may be called. Or the cell originating in those organization or they is processed with a trial compound. It compares with a non-processed control animal. Change of the symptom of each organ of this animal, an organization, a cell, and a disease etc., Especially A nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, Immunopathy, adrenal insufficiency, an eating disorder, obesity, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) Especially the increment in the amount of spontaneous behavior, muscular power lowering, etc. at night The myonosus, adrenal insufficiency, Prevention, therapy, and improvement effect of a trial compound can be examined by making the improvement effect of the increment in a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), or muscular power lowering into an index.

[0076]

As an approach of processing trial animals (OT7T 022 gene-expression insufficient nonhuman animal etc.) with a trial compound, internal use, an intravenous injection, etc. are used and it can choose suitably in accordance with the symptom of a trial animal, the property of a trial compound, etc., for example. Moreover, the dose of a trial compound can be suitably chosen in accordance with the property of a medication method and a trial compound etc.

For example, when screening prevention and therapy / improvement medicine of obesity, cholesterol load treatment can be performed to the OT7T 022 gene-expression insufficient nonhuman animal of this invention etc., a trial compound can be prescribed for the patient before cholesterol load treatment or after treatment, and it can screen by measuring the blood cholesterol level value of this animal, weight change, etc. with time. Moreover, medication, such as STZ or alloxan, can be performed to the OT7T 022 gene-expression insufficient nonhuman animal of this invention etc., a trial compound can be prescribed for the patient before sugar load treatment or after treatment, and it can screen by measuring the blood sugar level of this animal, weight change, etc. with time.

For example, in this screening approach, when a trial animal is medicated with a trial compound, the weight of this trial animal can choose this trial compound about 30% or more preferably about 10% or more as matter which has a therapy and a preventive

effect to obesity, when it decreases about 50% or more more preferably.
Moreover, when screening prevention and therapy / improvement medicine of a nociception failure, the OT7T 022 gene-expression insufficient nonhuman animal of this invention etc. can be medicated with a trial compound, and it can screen by measuring pain defense actions (an example, action to lick and which acts and riots, scratch action, etc.) of this animal etc. with time. Furthermore, after performing analgesic administration of morphine etc. to the OT7T 022 gene-expression insufficient nonhuman animal of this invention etc., a trial compound can be prescribed for the patient and it can screen by measuring pain defense actions (an example, action to lick and which acts and riots, scratch action, etc.) of this animal etc. with time.
For example, in this screening approach, when a trial animal is medicated with a trial compound, pain defense action of this trial animal can choose this trial compound about 30% or more preferably about 10% or more as matter which has a therapy and a preventive effect to a nociception failure, when it goes up about 50% or more more preferably.
[0077]
since it has prevention, the therapy, and the improvement effect of the disease which prevention and therapy / improvement medicine obtained using the screening approach of this invention contains the compound chosen from the above-mentioned trial compound, or its salt, and is caused by OT7T022 deficit, the disease caused by the deficit of OT7T022 is received -- safe -- low -- it is useful as remedies, such as toxic therapy, preventive, etc. Moreover, the compound guided from this compound can be used similarly.
As a salt of the compound obtained by this screening approach, the salt which can be permitted pharmacologically [a salt with a salt with an inorganic base, a salt with an organic base, a salt with an inorganic acid a salt with an organic acid, basicity, or acidic amino acid etc.], for example is raised.
As a suitable example of a salt with an inorganic base, an aluminum salt, ammonium salt, etc. are raised, for example to alkaline-earth-metal salts, such as alkali-metal salts, such as sodium salt and potassium salt, a calcium salt, and magnesium salt, and a list.
As a suitable example of a salt with an organic base, it is ********** with trimethylamine, triethylamine, pyridine, picoline, 2, 6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N, and N'-dibenzyl ethylenediamine etc., for example.
As a suitable example of a salt with an inorganic acid, a salt with a hydrochloric acid, a hydrobromic acid, a sulfuric acid, a phosphoric acid, etc. is raised, for example.
As a suitable example of a salt with an organic acid, a salt with a formic acid, an acetic acid, a propionic acid, a fumaric acid, oxalic acid, a tartaric acid, a maleic acid, a citric acid, a succinic acid, a malic acid, methansulfonic acid, benzenesulfonic acid, a benzoic acid, etc. is raised, for example.
As a suitable example of a salt with a basic amino acid, a salt with an arginine, a lysine, ORUCHININ, etc. is raised, for example, and a salt with an aspartic acid, glutamic acid, etc. is raised as a suitable example with acidic amino acid, for example.
[0078]
When using the compound obtained using the screening approach of this invention, or

its salt as above-mentioned therapy and preventive, it can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as the tablet and capsule which could carry out according to the stock-in-trade, for example, gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with this compound or its salt with the unit dosage gestalt required of the medicine manufacture implementation generally accepted with the support and the flavor agent which can be accepted pharmacologically, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. Capacity with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained.

As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth gum, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into said type of ingredient. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc.

[0079]

As a water solution for injection, the isotonic solutions (for example, D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the adjuvant of a physiological saline, grape sugar, or others etc. are mentioned, for example, and you may use together with a suitable solubilizing agent (for example, ethanol etc.), for example, alcohol, polyalcohols (for example, propylene glycol, a polyethylene glycol, etc.), nonionic surfactants (for example, polysorbate 80 TM, HCO-50, etc.), etc. As oily liquid, sesame oil, soybean oil, etc. are mentioned and you may use together with benzyl benzoate, benzyl alcohol, etc. as a solubilizing agent, for example. Moreover, you may blend with buffers (for example, a phosphate buffer, the sodium acetate buffer solution, etc.), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution.

Thus, the pharmaceutical preparation obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to Homo sapiens or homeotherms (for example, a mouse, Latt, a rabbit, a sheep, Buta, a cow, a horse, Tori, a cat, a dog, an ape, a chimpanzee, etc.), for example.

Although it is different with a symptom etc., in internal use, generally in adult's anorexia patient, about 0.1-100mg per day of about 1.0-50mg of doses of this compound or its salt is about 1.0-20mg more preferably (as weight of 60kg). Although a dose changes with the object organ for administration, a symptom, medication methods, etc. once [the] when prescribing a medicine for the patient parenterally, it is convenient to, usually prescribe more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection in adult's anorexia patient for example, in the form of injections (as weight of

60kg). The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

[0080]

[The screening approach B of this invention]

This invention medicates the OT7T 022 gene-expression insufficient nonhuman animal of this invention with a trial compound, and offers the screening approach of the compound which promotes or checks a promotor's activity over the gene of this invention characterized by detecting the manifestation of a reporter gene, or its salt.

In the above-mentioned screening approach, as an OT7T 022 gene-expression insufficient nonhuman animal of this invention, it is inactivated when OT7T022 gene introduces a reporter gene, and what this reporter gene may discover under a promotor's control to OT7T022 gene is used also in the OT7T 022 gene-expression insufficient nonhuman animal of above mentioned this invention.

The same thing as the above is raised as a trial compound.

The same thing as the above is used as a reporter gene, and a beta-galactosidase gene (lacZ), a fusibility alkaline phosphatase gene, or a luciferase gene is suitable.

A promotor's activity is detectable by tracing the manifestation of the matter with which a reporter gene carries out the code of the OT7T022 gene since a reporter gene exists under a promotor's rule to OT7T022 gene for the OT7T 022 gene-expression insufficient nonhuman animal of this invention permuted by the reporter gene.

[0081]

For example, when a part of OT7T 022 gene field is permuted with the beta-galactosidase gene (lacZ) of the Escherichia coli origin, originally the beta-galactosidase is discovered in the organization which does OT7T022 gene expression instead of OT7T022. The manifestation condition of OT7T022 animal in the living body is observable simple by dyeing using the reagent which follows, for example, serves as a substrate of beta-galactosidase like 5-BUROMO-4-chloro-3-indolyl-beta-galactopyranoside (X-gal). What is necessary is to be the stain solution which fixes an OT7T 022 genetic-defect mouse or its organization intercept by glutaraldehyde etc., and specifically contains X-gal after washing with a phosphoric-acid buffer physiological salt solution (PBS), to be a room temperature or near 37 degree C, to stop a beta-galactosidase reaction and just to observe coloration by washing the preparation with 1 mM EDTA/PBS solution, about 30 minutes thru/or after making it react for 1 hour. Moreover, according to a conventional method, mRNA which carries out the code of the lacZ may be detected.

For example, when a trial animal is medicated with a trial compound in this screening approach, The manifestation of reporter protein preferably about 10% or more About 30% or more, When it increases about 50% or more more preferably, it can choose as the compound which promotes promotor activity [as opposed to OT7T022 gene for this trial compound], or its salt. When a trial animal is medicated with a trial compound, the manifestation of reporter protein About 10% or more, Preferably, about 30% or more, when it decreases about 50% or more more preferably, it can choose as the compound which checks promotor activity [as opposed to OT7T022 gene for this trial compound], or its salt.

The compound obtained using the above-mentioned screening approach or its salt is the matter chosen from the above-mentioned trial compound, and is the compound

which promotes or checks the promotor activity over OT7T022 gene, or its salt.
The acid addition salt which a salt with acids (the example, inorganic acid, etc.), bases, etc. (an example, organic acid, etc.) which are permitted physiologically is used as a salt of the compound obtained by this screening approach, and is especially permitted physiologically is desirable. As such a salt, a salt with inorganic acids (for example, a hydrochloric acid, a phosphoric acid, a hydrobromic acid, a sulfuric acid, etc.) or a salt with organic acids (for example, an acetic acid, a formic acid, a propionic acid, a fumaric acid, a maleic acid, a succinic acid, a tartaric acid, a citric acid, a malic acid, oxalic acid, a benzoic acid, methansulfonic acid, benzenesulfonic acid, etc.) is used, for example.
[0082]
The compound which promotes the promotor activity over OT7T022 gene, or its salt Since the manifestation of OT7T022 can be promoted and the function of OT7T022 can be promoted For example, a nociception failure, an eye disease, a hypophysis disease, the myonosus, a heart disease, a hemopathy, Kidney disease, immunopathy, adrenal insufficiency, an eating disorder, the emotional disorder, schizophrenia, A depression, uneasy **, and reproductive function failure, obesity, a convulsion, epilepsy, aggression action, A gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, the amount of spontaneous behavior (especially) Especially the increment in the amount of spontaneous behavior, muscular power lowering, etc. at night The myonosus, adrenal insufficiency, It can be used as remedies, such as prevention and therapy / improvement agent of diseases, such as an increment or muscular power lowering of a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior).
On the other hand, the compound which checks the promotor activity over OT7T022 gene, or its salt Since the manifestation of OT7T022 can be checked and the function of OT7T022 can be checked For example, the myonosus, adrenal insufficiency, temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially) It can be used at night as remedies, such as prevention and therapy / improvement agent of reduction of the amount of spontaneous behavior, a painkiller, an analgesic action accelerator of morphine, a morphine resistance evasion agent, and a morphine dependency evasion agent.
Furthermore, the compound guided from the compound obtained by the above-mentioned screening can be used similarly.
[0083]
The remedy containing the compound obtained by this screening approach or its salt can be manufactured like the remedy containing the compound obtained by the above mentioned screening approach A, or its salt.
Thus, the pharmaceutical preparation obtained is safe, and since it is low toxicity, it can be prescribed for the patient to Homo sapiens or mammalians (for example, Latt, a mouse, a guinea pig, a rabbit, a sheep, Buta, a cow, a horse, a cat, a dog, an ape, etc.), for example.
Although it is different with the administration root an object disease and for administration etc., the dose of this compound or its salt For example, when

administering orally the matter which promotes the promotor activity over OT7T022 gene for the purpose of [of a nociception failure] a therapy, generally it sets to an adult patient (as weight of 60kg). This compound or about 0.1-100mg of about 1.0-50mg of about 1.0-20mg of its salt are more preferably prescribed for the patient per day. Although this compound or the 1-time dose of the salt changes with object diseases for administration etc. when prescribing a medicine for the patient parenterally For example, when an adult patient is usually medicated with the compound which promotes the promotor activity over OT7T022 gene for the purpose of [of a nociception failure] a therapy, or its salt in the form of injections (as weight of 60kg), It is convenient per day to prescribe more preferably about about 0.01-30mg about about 0.1-20mg about about 0.1-10mg for the patient for this matter by the intravenous injection. The amount which converted into per weight of 60kg also in other animals can be prescribed for the patient.

[0084]

Thus, the OT7T 022 gene-expression insufficient nonhuman animal of this invention is very useful when screening the compound which promotes or checks a promotor's activity over OT7T022 gene, or its salt, and it can contribute to cause investigation of the various diseases resulting from OT7T 022 gene-expression incompetence, or development of prevention and therapy / improvement medicine greatly.

Moreover, if the gene which carries out the code of the various protein to the lower stream of a river is connected using DNA containing the promoterregion of OT7T022 gene, this is poured into the ootid of an animal and the so-called transgenic animal (gene transfer animal) is created, the peptide will be made to compound specifically and it will also become possible to consider an operation with the living body. The still more suitable reporter gene for the above-mentioned promotor part is combined, and if a cell strain which this discovers is established, it can be used as a retrieval system of a low molecular weight compound with the operation which promotes or controls specifically the production capacity in the inside of the body of OT7T022 themselves.

[0085]

(10) The break-through approach of the operation mechanism of various drugs

By using OT7T022, it can check whether various drugs demonstrate the pharmacology effectiveness through OT7T022.

Namely, this invention,

(1) The nociception failure, eye disease which are characterized by using OT7T022, A hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, adrenal insufficiency, An eating disorder, obesity, emotional-disorder, schizophrenia, depression, uneasy **, and reproductive function failure, Obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, The increment in a decrease of platelets and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), muscular power lowering, How to check that analgesic [to reduction of temperature reduction, the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially night the amount of spontaneous behavior) / prevention and therapy / improvement medicine and analgesic], the analgesic action acceleration medicine of morphine, morphine resistance evasion medicine, etc. combine with OT7T022,

(2) The nociception failure, eye disease which are characterized by using OT7T022, A

hypophysis disease, the myonosus, a heart disease, a hemopathy, kidney disease, immunopathy, adrenal insufficiency, An eating disorder, obesity, emotional-disorder, schizophrenia, depression, uneasy **, and reproductive function failure, Obesity, a convulsion, epilepsy, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, The increment in a decrease of platelets and the amount of spontaneous behavior (especially night the amount of spontaneous behavior), muscular power lowering, etc., How to check especially that prevention and therapy / improvement medicine to an increment or muscular power lowering of the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior (especially night the amount of spontaneous behavior) is the agonist to OT7T022,
(3) How to check that analgesic [to reduction of the myonosus and adrenal insufficiency which are characterized by using OT7T022, temperature reduction the increment in a white blood cell count, the increment in a platelet count, or the amount of spontaneous behavior (especially night the amount of spontaneous behavior) / prevention and therapy / improvement medicine and analgesic], the analgesic action acceleration medicine of morphine, morphine resistance evasion medicine, etc. are the antagonists to OT7T022,
(4) Offer the screening approach given [above-mentioned] in (1) - (3) characterized by measuring the amount of association of each medicine at the time of contacting each medicine to OT7T022, and OT7T022.
In the screening approach of the compound to which the affinity of the above mentioned RFRP and OT7T022 is changed, or its salt, this symptom can be replaced with a trial compound and can be enforced by using the above-mentioned drug. Moreover, in the kit for screening of the compound to which the affinity of the above mentioned RFRP and OT7T022 is changed, the kit for symptoms of this invention is replaced with a trial compound, and contains the above-mentioned drug.
Thus, it can check that the various drugs in the middle of marketing or development demonstrate the pharmacology effectiveness through OT7T022 by using the symptom of this invention.
[0086]
In this description and a drawing, when displaying a base, amino acid, etc. by the code, the following of the example is carried out based on the code by IUPAC-IUB Commission on Biochemical Nomenclature, or the common use code in the field concerned. Moreover, especially when there may be an optical isomer about amino acid, L bodies shall be shown if not shown clearly.
DNA : deoxyribonucleic acid
cDNA : complementary deoxyribonucleic acid
A : adenine
T : thymine
G : guanine
C : cytosine
I : inosine
R : an adenine (A) or a guanine (G)
Y : a thymine (T) or a cytosine (C)
M : an adenine (A) or a cytosine (C)

K : a guanine (G) or a thymine (T)
S : a guanine (G) or a cytosine (C)
W : an adenine (A) or a thymine (T)
B : a guanine (G), a guanine (G), or a thymine (T)
D : an adenine (A), a guanine (G), or a thymine (T)
V : an adenine (A), a guanine (G), or cytosine (C)
N : an adenine (A), a guanine (G), a cytosine (C), a thymine (T), or the base of unknown or others
RNA : ribonucleic acid
mRNA : messenger RNA
dATP : deoxyadenosine triphosphoric acid
dTTP : deoxythymidine triphosphoric acid
dGTP : deoxyguanosine triphosphoric acid
dCTP : deoxycytidine triphosphoric acid
ATP : adenosine triphosphate
EDTA : ethylenediaminetetraacetic acid
SDS : sodium dodecyl sulfate
BHA : benzhydryl amine
pMBHA : p-methyl benzhydryl amine
Tos :p-toluene sulfonyl
Bzl : benzyl
Bom : benzyloxymethyl
Boc :t-butyloxy carbonyl
DCM : dichloromethane
HOBt : 1-hydroxy bends triazole
DCC : N and N'-dicyclohexylcarbodiimide
TFA : trifluoroacetic acid
DIEA : diisopropyl ethylamine
Gly : glycine
Ala or A : Alanine
Val or V : Valine
Leu or L : Leucine
Ile or I : Isoleucine
Ser or S : Serine
Thr or T : Threonine
Cys or C : Cysteine
Met or M : Methionine
Glu or E : Glutamic acid
Asp or D : Aspartic acid
Lys or K : Lysine
Arg or R : Arginine
His or H : Histidine
Phe or F : Phenylalanine
Tyr or Y : Thyrosin
Trp or W : Tryptophan
Pro or P : Proline
Asn or N : Asparagine

Gln or Q : Glutamine
pGlu : pyroglutamic acid
[0087]
The array number of the array table of this application description shows the following arrays.
[array number: 1]
The amino acid sequence (Homo sapiens mold) of RFRP is shown.
[array number: 2]
Array number: The base sequence of DNA which carries out the code of the RFRP which has the amino acid sequence expressed with 1 is shown.
[array number: 3]
The amino acid sequence (Homo sapiens mold) of RFRP is shown.
[array number: 4]
Array number: The base sequence of DNA which carries out the code of the RFRP which has the amino acid sequence expressed with 3 is shown.
[array number: 5]
The amino acid sequence (cow mold) of RFRP is shown.
[array number: 6]
Array number: The base sequence of DNA which carries out the code of the RFRP which has the amino acid sequence expressed with 5 is shown.
[array number: 7]
The amino acid sequence (Latt mold) of RFRP is shown (before RIKURONINGU).
[array number: 8]
Array number: The base sequence of DNA which carries out the code of the RFRP which has the amino acid sequence expressed with 7 is shown.
[array number: 9]
The amino acid sequence (mouse mold) of RFRP is shown.
[array number: 10]
Array number: The base sequence of DNA which carries out the code of the RFRP which has the amino acid sequence expressed with 9 is shown.
[array number: 11]
The amino acid sequence of Latt origin G protein conjugation mold receptor protein rOT7T022 is shown.
[array number: 12]
The base sequence of cDNA which carries out the code of Latt origin G protein conjugation mold receptor protein rOT7T022 is shown.
[array number: 13]
The amino acid sequence of a RFRP partial peptide is shown.
[array number: 14]
The amino acid sequence of a RFRP partial peptide is shown.
[array number: 15]
The amino acid sequence of a RFRP partial peptide is shown.
[array number: 16]
Array number: The base sequence which carries out the code of the peptide containing the 81st - (Met) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with 1 is shown.
[array number: 17]

Array number: The base sequence which carries out the code of the peptide containing the 101st - (Ser) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 1 is shown.
[array number: 18]
Array number: The base sequence which carries out the code of the peptide containing the 124th - (Val) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 1 is shown.
[array number: 19]
Array number: The base sequence which carries out the code of the peptide containing the 1st - (Met) the 92nd amino acid sequence (Phe) of the amino acid sequence expressed with 1 is shown.
[array number: 20]
Array number: The base sequence which carries out the code of the peptide containing the 1st - (Met) the 112nd amino acid sequence (Ser) of the amino acid sequence expressed with 1 is shown.
[array number: 21]
Array number: The base sequence which carries out the code of the peptide containing the 1st - (Met) the 131st amino acid sequence (Phe) of the amino acid sequence expressed with 1 is shown.
[array number: 22]
The amino acid sequence (Latt mold) of RFRP is shown (after RIKURONINGU).
[array number: 23]
Array number: The base sequence of DNA which carries out the code of the RFRP which has the amino acid sequence expressed with 22 is shown.
[array number: 24]
The amino acid sequence which carries out the code of Homo sapiens origin G protein conjugation mold receptor protein hOT7T022 is shown.
[array number: 25]
Array number: The base sequence of DNA which carries out the code of the hOT7T022 which have the amino acid sequence expressed with 24 is shown.
[array number: 26]
Array number: The base sequence of DNA which carries out the code of the hOT7T022 which have the amino acid sequence expressed with 24 is shown.
[array number: 27]
The partial amino acid sequence of mouse origin G protein conjugation mold receptor protein OT7T022 is shown.
[array number: 28]
Array number: The base sequence of the genomic DNA which carries out the code of the mouse origin OT7T022 which have the amino acid sequence expressed with 27 is shown.
[array number: 29]
The base sequence of the primer used in the example 3 is shown.
[array number: 30]
The base sequence of the primer used in the example 3 is shown.
[array number: 31]
The base sequence of the primer used in the example 3 is shown.
[array number: 32]

Array number: The base sequence of the genomic DNA which carries out the code of the mouse origin OT7T022 which have the amino acid sequence expressed with 27 is shown. Array number: It is the array which specified n in the base sequence expressed with 28.

[0088]

Transformant Escherichia coli JM109/pKS-OT7T0221 obtained in the below-mentioned example 1 are 1-1-1, Higashi, Tsukuba-shi, Ibaraki-ken from October 17, 2002. The independent administrative agency National Institute of Advanced Industrial Science and Technology of a center 6th (zip code 305-8566) It ****s in the patent living thing deposition pin center,large as deposition number FERM BP-8210.

Transformant Escherichia coli JM109/pKS-OT7T0222 obtained in the below-mentioned example 1 are 1-1-1, Higashi, Tsukuba-shi, Ibaraki-ken from October 17, 2002. The independent administrative agency National Institute of Advanced Industrial Science and Technology of a center 6th (zip code 305-8566) It ****s in the patent living thing deposition pin center,large as deposition number FERM BP-8211.

Transformant Escherichia coli JM109/pKS-OT7T0223 obtained in the below-mentioned example 1 are 1-1-1, Higashi, Tsukuba-shi, Ibaraki-ken from October 17, 2002. The independent administrative agency National Institute of Advanced Industrial Science and Technology of a center 6th (zip code 305-8566) It ****s in the patent living thing deposition pin center,large as deposition number FERM BP-8212.

Transformant Escherichia coli JM109/pKS-OT7T0224 obtained in the below-mentioned example 1 are 1-1-1, Higashi, Tsukuba-shi, Ibaraki-ken from October 17, 2002. The independent administrative agency National Institute of Advanced Industrial Science and Technology of a center 6th (zip code 305-8566) It ****s in the patent living thing deposition pin center,large as deposition number FERM BP-8213.

Transformant Escherichia coli JM109/p022Tgv-2 obtained in the below-mentioned example 2 are 1-1-1, Higashi, Tsukuba-shi, Ibaraki-ken from October 17, 2002. The independent administrative agency National Institute of Advanced Industrial Science and Technology of a center 6th (zip code 305-8566) It ****s in the patent living thing deposition pin center,large as deposition number FERM BP-8214.

[0089]

[Example]

Although an example is given to below and this invention is explained to it still more concretely, this invention is not limited to it. In addition, the genetic manipulation method using Escherichia coli followed the approach indicated by molecular cloning (Molecular cloning).

[0090]

Example 1 Cloning of mouse OT7T022

Latt OT7T022 cDNA (array number : 12 WO 00/No. 29441) was used as the probe. Latt cDNA The DNA fragment of 580-1170 bp was produced as a probe (PCR-DIG a probe composition kit, the Roche diamond GONISU tex company). The probe is used and it is 1st to a mouse 129SvJ lambda genomic library (Stratagene). As a result of performing plaque hybridization, six electropositive plaques were obtained. 1st They

are 2nd(s) to six electropositive plaques obtained by plaque hybridization. Plaque hybridization was performed and two electropositive clones were isolated.
It is abbreviation as a result of performing Southern hybridization. 4.5 kbp It is OT7T022 to a Bam HI fragment. It became clear that a coding region existed. As a result of a sequencer's (PerkinElmer's, Inc.) investigating a base sequence for the DNA fragment which carried out cloning with the conventional method, it is 3' of Latt OT7T022. Side It is the fragment which has an exon (0.9 kbp) and 94% of homology, and is mouse OT7T022 genome. It checked that it was DNA. Bam HI which furthermore carries out the code of OT7T022 Bam HI of 5 'side 3.8 kbp and 3' side 5.5 kbp of a fragment Cloning of the fragment was carried out. It is 3' by Southern analysis. Side More than as for 1.8 kbp, the exon showed that one exon existed in the upstream which got used (array number: 28 or array number : 32).
Mouse OT7T022 genome The transformation of the fragment of DNA was carried out to 109 shares of Escherichia coli JM, and transformant Escherichia coli JM109/pKS-OT7T0221, transformant Escherichia coli JM109/pKS-OT7T0222, transformant Escherichia coli JM109/pKS-OT7T0223, and transformant Escherichia coli JM109/pKS-OT7T0224 were acquired.
[0091]
Example 2 Construction of a targetting vector, and production of ES homologous recombination
construction of an OT7T 022 targetting vector, and 3 -- '5 of a side exon' Side a Sac I-Bam HI fragment (3.2 kbp) and 3' -- a side BstEII-Xho I fragment (5.2 kbp), a neomycin resistance gene, and a diphtheria toxin gene -- using -- carrying out -- 3' Side Deletion of the exon 1.2 kbp was carried out. OT7T022 Construction of targetting vector p022Tgv-2 was ended (drawing 1). OT7T022 The transformation of targetting vector p022Tgv-2 was carried out to 109 shares of Escherichia coli JM, and transformant Escherichia coli JM109/p022Tgv-2 were acquired. It is the mouse 129SvEv system origin ES about an OT7T 022 targetting vector. It introduced into the cell (2.2 AB(s)) by electroporation. Electroporation uses a gene pulsar electroporation system (Bio-Rad make), and is an electrical potential difference. 230 V, Resistance 500 muF and DNA solution concentration 30 It carried out by setting up mug/ml of conditions.
The transgenics experiment was able to be conducted 3 times and 1000 or more shares of neomycin resistant strains were able to be obtained, respectively. 739 shares of neomycin resistant strains obtained by targeting vector p022Tgv-2 were cultivated on 24 well plate, and ethanol precipitate extracted DNA after -70-degree-C freeze thawing and Proteinase K processing.
The BamHI-Xho I 600 bp fragment by the side of 5' (field of the outside of the genome used for the targeting vector) was used as the probe to 595 shares of genomes among those, and Southern hybridization was performed. Consequently, the band of 5.4 kb presumed to be homologous recombinant by six shares was seen (wild type 3.8kb). DNA considered to be homologous recombinant Six sorts of embryonic stem cell stocks (No.126, 130, 283, 491, 532, 545) with which the fragment was detected ******** -- Southern analysis was performed for reconfirmation. DNA after cultivating each cell which carried out cryopreservation It extracted, the above-mentioned 600 bp fragment was used as the probe after Bam HI-Xho I cutting, and Southern hybridization was performed. Consequently, in all cells, the 5.4 kb

fragment (as for a wild type, only a 3.8 kb fragment is observed) has been reconfirmed. Moreover, although the wild type and the band seen [recombinant] were near 2 kb as a result of performing Southern hybridization by using a probe as a neomycin resistance gene, the band of 5.4 kb could be checked only to recombinant and it has checked that six sorts of all embryonic stem cells were homologous recombinant. Among these six homologous recombinant, about three homologous recombinant cell strains (No.130, 283, 532) whose growth was good, for karyotype analysis, the bottom of feeder cell existence and an embryonic stem cell were cultivated until it became confluent in 25cm two flasks, colcemid was added (the 0.1microg [/ml] last cell density), and 37 degrees C was cultivated for 2 hours. PBS -- after washing and trypsinization -- carrying out -- centrifugal -- it took 1000 rpm for 5 minutes. 0.075M KCl 4ml was added on the pellet, and Carnoy's fluid (acetic acid: methanol ratio = 1:3) was quietly suspended after one-drop addition in cell suspension after 20-minute neglect at the room temperature. It carried out for room temperature neglect 60 minutes, and centrifugal was carried out, the pellet was quietly suspended by 4ml of Carnoy's fluid, and room temperature neglect was carried out further. It repeated about 5 times for 30 minutes. 2-3ml of Carnoy's fluid is added to an after [centrifugal] pellet, it prepares to moderate concentration, and they are 2-3 drops about cell suspension on a slide glass. It was dropped. The GIMUZA solution dyed 3% after the air dried, and chromosome observation in the middle of a mitotic phase was performed under the microscope. The percentage of a cell of having a result and a normal karyotype was 61 - 69%. Since the abnormalities in a karyotype of three homologous recombinant cell strains were not seen, cell strain No.283 with good fecundity were selected.

[0092]

Example 3 Production of a knockout mouse

Injection to C57BL / six-line mouse blastocyst was performed for homologous recombination cell strain No.283 with the conventional method. The blastocyst by which injection was carried out was impregnated by transplanting to the pseudopregnancy mouse oviduct obtained by crossing with a vasoligature mouse separately. About 283 shares, the abbreviation one half of a transplantation germ was produced as offspring, and 75% was a chimeric mouse. The male chimeric mouse was crossed with C57BL / six-line female mouse, and performed the germ cell line shift by offspring, and acquisition of a hetero mouse.

A chimera and C57BL It is 51 by mating with a system mouse. Embryonic stem cell of ** The origin mouse was obtained. It is a genome from a mouse tail. DNA is refined and it is PCR first. The conditions of a genotype judging to depend were examined. a primer is common in 3' side (AGGTGCTCAGTGTGTAGAAGTGG (array ****: 29)) of the field which carried out targeting as a result of examination -- carrying out -- moreover, 5' -- a side as an object for wild type detection The near [a termination codon] array in the field made to suffer a loss (ATCCCAGCCTGGAACATTTTGAGG (array number: 30)), It is a neomycin resistance intragenic array as an object for variant detection. (TCATAGCCGAATACGGTCTCCAC (array number: 31)) Carrying out, polymerase used KOD-plus- (Toyobo Co., Ltd. make). A wild type is 300 bp, if only a 300 bp fragment is detected and it is a hetero deficit individual. It reaches. PCR designed so that a 600 bp fragment could be detected The hetero deficit mouse was able to be obtained as a result of the gene judging to depend. Next, Southern

hybridization was performed and the genetic defect was checked.
[0093]
Example 4 Change of organ weight
It dissected by slaughtering the 8 weeks old individual of after the birth of a male gay deficit mouse by cervical dislocation. Each main organs were taken out and the gravimetry was performed. Consequently, in organ weight, the difference was not accepted in a wild type mouse and a gay deficit mouse. In the result of organ weight measurement of 13 weeks old of after the birth, the significant increment was seen with the gay deficit mouse compared with the wild type mouse in the thymus gland.
[0094]
Example 5 Weight, the amount of drinking water, food consumption
A change with time was investigated about the weight, the amount of baiting, and the amount of drinking water of a gay deficit mouse. Compared with the wild type mouse, the difference was not seen for weight change of an after [ablactation] male gay deficit mouse. In a change of the amount of baiting, and the amount of drinking water with time, the wild type mouse and the difference were not regarded as a male-and-female nature gay deficit mouse, either.
[0095]
Example 6 Behavioral abnormality
Trivial movement and appearance observation were performed based on the approach of Irwin (1968). Consequently, in the gay deficit mouse (the inside of two maleness, two examples) of age, the abnormal gait was observed for after-the-birth six months. The opisthoporeia was seen in the gay deficit mouse (7 weeks old) of another lot, and a gait abnormality which drags a hind foot was also observed. Although the individual which furthermore shows a tremor or a convulsion was seen, as for the extent, the difference between individuals was seen. These behavioral abnormalities were observed in the hybrid of C57BL/6J and 129SvEv systems.
[0096]
Example 7 Reaction to a noxious stimulus
In order to evaluate the reactivity over a heat noxious stimulus in the approach (Wilson SG, Mogil JS.Behav Brain Res 125:65-73, 2001) used with the mouse in order to evaluate about the reaction to a noxious stimulus, the hot plate trial (it is also called a hot-platen method) was performed.
The hot plate trial was performed using the commercial hot plate type analgesic effect measuring device. At first, the with a diameter height [20cm height of 15cm] glass cylinder was placed on the hot plate heated at 55 degrees C, the mouse was put in in the cylinder, and or the mouse licked the hind foot, time amount until action of saltation etc. appears was measured. Consequently, or it licked the hind foot in the male gay deficit mouse, saltation time amount was delayed intentionally.
[0097]
Example 8 Aggressive behavior
When behavior observation of a male gay deficit mouse was performed, the aggression over other sex mice was observed rather than the wild type mouse. It sets to some [further] mice and is tail rattling at the time of handling. It was observed and the slight Straub's tail reaction was observed at the time of breeding. the cage for observation -- a male mouse -- a two-piece body -- the method (Nature 378:383-386, 1995) of putting in and observing mutual aggressive behavior and (Nature 265:1875-1878, 1994)

the attack response latent time of a gay deficit mouse were measured. Consequently, the latent time to aggressive behavior was intentionally short with the gay deficit mouse. These actions were observed in the hybrid of C57BL/6J and 129SvEv systems.

[0098]

Example 9 Morphine administration trial

Time amount until it is immersed in the cistern into which 52-degree-C molten bath went using the male gay deficit mouse of C57BL / 11 weeks old of 6J congenic systems from a tail head to the place of 3cm and a tail comes out of a cistern to it was evaluated as responsibility over a heat noxious stimulus (it is also called tail immersion test and a warm water method).

The maximum time amount (cut off time) of an experiment was made into 20 seconds. The gay deficit mouse and the wild type mouse of C57BL / 11 weeks old of 6J congenic systems experimented by dividing into a vehicle administration group and a morphine administration group, respectively. The significant difference was not seen by the reaction mean time in all groups as a result of performing above-mentioned tail immersion test before administration. Next, tail immersion test was carried out for morphine (kg 5mg per weight), or vehicle by the approach that it is the same after intraperitoneal administration, 15 minutes, and 30 minutes. The reaction time of a morphine administration male gay deficit mouse group became longer than other groups. Although the difference was in the reaction latency of a wild type mouse and a gay deficit mouse at tail immersiontest before morphine administration, in the gay deficit mouse which carried out morphine administration to having compared the wild type mouse which carried out morphine administration after 15 minutes and 30 minutes, having compared latency before administration, and having extended intentionally, after morphine administration did not change latency of a reaction to thermal stimulation to before morphine administration.

[0099]

[Effect of the Invention]

DNA which carries out the code of RFRP and OT7T022, or them is useful as prevention and therapy / improvement medicine, such as an increment in the myonosus, adrenal insufficiency, a convulsion, aggression action, a gait abnormality, the feverscence, white blood cell count reduction, a decrease of platelets, and the amount of spontaneous behavior, or muscular power lowering.

Moreover, the O7T 022 gene-expression insufficient nonhuman animal is useful to screening of prevention and therapy / improvement medicine of the above-mentioned disease.

[0100]

[Layout Table]

[Sequence Listing]

〈110〉 Takeda Chemical Industries, Ltd.

〈120〉 Novel Use of RFRP and OT7T022

〈130〉 B03176

〈150〉 JP 2002-232684

〈151〉 2002-08-09

〈160〉 32

〈210〉 1

〈211〉 180

〈212〉 PRT

〈213〉 Human

〈400〉 1

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Met Glu Ile Ile Ser Ser Lys Leu Phe Ile Leu Leu Thr Leu Ala Thr
 1               5                  10                  15
Ser Ser Leu Leu Thr Ser Asn Ile Phe Cys Ala Asp Glu Leu Val Met
            20                  25                  30
Ser Asn Leu His Ser Lys Glu Asn Tyr Asp Lys Tyr Ser Glu Pro Arg
        35                  40                  45
Gly Tyr Pro Lys Gly Glu Arg Ser Leu Asn Phe Glu Glu Leu Lys Asp
    50                  55                  60
Trp Gly Pro Lys Asn Val Ile Lys Met Ser Thr Pro Ala Val Asn Lys
65                  70                  75                  80
Met Pro His Ser Phe Ala Asn Leu Pro Leu Arg Phe Gly Arg Asn Val
                85                  90                  95
Gln Glu Glu Arg Ser Ala Gly Ala Thr Ala Asn Leu Pro Leu Arg Ser
            100                 105                 110
Gly Arg Asn Met Glu Val Ser Leu Val Arg Arg Val Pro Asn Leu Pro
        115                 120                 125
Gln Arg Phe Gly Arg Thr Thr Thr Ala Lys Ser Val Cys Arg Met Leu
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    130                 135                 140
Ser Asp Leu Cys Gln Gly Ser Met His Ser Pro Cys Ala Asn Asp Leu
145                 150                 155                 160
Phe Tyr Ser Met Thr Cys Gln His Gln Glu Ile Gln Asn Pro Asp Gln
                165                 170                 175
Lys Gln Ser Arg
            180
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〈210〉 2
〈211〉 540
〈212〉 DNA
〈213〉 Human
〈400〉 2

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tatgacaaat attctgagcc tagaggatac ccaaaagggg aaagaagcct caattttgag 180
gaattaaaag attggggacc aaaaaatgtt attaagatga gtacacctgc agtcaataaa 240
atgccacact cctttcgccaa cttgccattg agatttggga ggaacgttca agaagaaaga 300
agtgctggag caacagccaa cctgcctctg agatctgga agaaatatgga ggtgagcctc 360
gtgagacgtg ttcctaacct gccccaaagg tttgggagaa caacaacagc caaaagtgtc 420
tgcaggatgc tgagtgattt gtgtcaagga tccatgcatt caccatgtgc caatgactta 480
ttttactcca tgacctgcca gcaccaagaa atccagaatc ccgatcaaaa acagtcaagg 540

〈210〉 3
〈211〉 196
〈212〉 PRT
〈213〉 Human
〈400〉 3

Met Glu Ile Ile Ser Ser Lys Leu Phe Ile Leu Leu Thr Leu Ala Thr
1 5 10 15
Ser Ser Leu Leu Thr Ser Asn Ile Phe Cys Ala Asp Glu Leu Val Met
20 25 30
Ser Asn Leu His Ser Lys Glu Asn Tyr Asp Lys Tyr Ser Glu Pro Arg
35 40 45
Gly Tyr Pro Lys Gly Glu Arg Ser Leu Asn Phe Glu Glu Leu Lys Asp
50 55 60
Trp Gly Pro Lys Asn Val Ile Lys Met Ser Thr Pro Ala Val Asn Lys
65 70 75 80
Met Pro His Ser Phe Ala Asn Leu Pro Leu Arg Phe Gly Arg Asn Val
85 90 95
Gln Glu Glu Arg Ser Ala Gly Ala Thr Ala Asn Leu Pro Leu Arg Ser
100 105 110
Gly Arg Asn Met Glu Val Ser Leu Val Arg Arg Val Pro Asn Leu Pro

115 120 125

Gln Arg Phe Gly Arg Thr Thr Thr Ala Lys Ser Val Cys Arg Met Leu

130 135 140

Ser Asp Leu Cys Gln Gly Ser Met His Ser Pro Cys Ala Asn Asp Leu

145 150 155 160

Phe Tyr Ser Met Thr Cys Gln His Gln Glu Ile Gln Asn Pro Asp Gln

165 170 175

Lys Gln Ser Arg Arg Leu Leu Phe Lys Lys Ile Asp Asp Ala Glu Leu

180 185 190

Lys Gln Glu Lys

195

〈210〉 4

〈211〉 588

〈212〉 DNA

〈213〉 Human

〈400〉 4

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acatcaaaca ttttttgtgc agatgaatta gtgatgtcca atcttcacag caaagaaaat 120
tatgacaaat attctgagcc tagaggatac ccaaaagggg aaagaagcct caattttgag 180
gaattaaaag attggggacc aaaaaatgtt attaagatga gtacacctgc agtcaataaa 240
atgccacact ccttcgccaa cttgccattg agatttggga ggaacgttca agaagaaaga 300
agtgctggag caacagccaa cctgcctctg agatctggaa gaaatatgga ggtgagcctc 360
gtgagacgtg ttcctaacct gccccaaagg tttgggagaa caacaacagc caaaagtgtc 420
tgcaggatgc tgagtgattt gtgtcaagga tccatgcatt caccatgtgc caatgactta 480
ttttactcca tgacctgcca gcaccaagaa atccagaatc ccgatcaaaa acagtcaagg 540
agactgctat tcaagaaaat agatgatgca gaattgaaac aagaaaaa 588

〈210〉 5

〈211〉 196

〈212〉 PRT

〈213〉 Bovine

〈400〉 5

Met Glu Ile Ile Ser Leu Lys Arg Phe Ile Leu Leu Met Leu Ala Thr
1 5 10 15
Ser Ser Leu Leu Thr Ser Asn Ile Phe Cys Thr Asp Glu Ser Arg Met
20 25 30
Pro Asn Leu Tyr Ser Lys Lys Asn Tyr Asp Lys Tyr Ser Glu Pro Arg
35 40 45
Gly Asp Leu Gly Trp Glu Lys Glu Arg Ser Leu Thr Phe Glu Glu Val
50 55 60
Lys Asp Trp Ala Pro Lys Ile Lys Met Asn Lys Pro Val Val Asn Lys
65 70 75 80
Met Pro Pro Ser Ala Ala Asn Leu Pro Leu Arg Phe Gly Arg Asn Met
85 90 95

Glu Glu Glu Arg Ser Thr Arg Ala Met Ala His Leu Pro Leu Arg Leu
100 105 110

Gly Lys Asn Arg Glu Asp Ser Leu Ser Arg Trp Val Pro Asn Leu Pro
115 120 125
Gln Arg Phe Gly Arg Thr Thr Thr Ala Lys Ser Ile Thr Lys Thr Leu
130 135 140
Ser Asn Leu Leu Gln Gln Ser Met His Ser Pro Ser Thr Asn Gly Leu
145 150 155 160
Leu Tyr Ser Met Ala Cys Gln Pro Gln Glu Ile Gln Asn Pro Gly Gln
165 170 175
Lys Asn Leu Arg Arg Arg Gly Phe Gln Lys Ile Asp Asp Ala Glu Leu
180 185 190
Lys Gln Glu Lys
195

〈210〉 6
〈211〉 588
〈212〉 DNA

〈213〉 Bovine

〈400〉 6

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tatgacaaat attccgagcc tagaggagat ctaggctggg agaaagaaag aagtcttact 180
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tccagatggg tcccaaatct gccccagagg tttggaagaa caacaacagc caaaagcatt 420
accaagaccc tgagtaattt gctccagcag tccatgcatt caccatctac caatgggcta 480
ctctactcca tggcctgcca gccccaagaa atccagaatc ctggtcaaaa gaacctaagg 540
agacggggat tccagaaaat agatgatgca gaattgaaac aagaaaaa 588

〈210〉 7

〈211〉 203

〈212〉 PRT

〈213〉 Rat

〈400〉 7

Met Glu Ile Ile Ser Ser Lys Arg Phe Ile Leu Leu Thr Leu Ala Thr
1 5 10 15
Ser Ser Phe Leu Thr Ser Asn Thr Leu Cys Ser Asp Glu Leu Met Met
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Pro His Phe His Ser Lys Glu Gly Tyr Gly Lys Tyr Tyr Gln Leu Arg
35 40 45
Gly Ile Pro Lys Gly Val Lys Glu Arg Ser Val Thr Phe Gln Glu Leu
50 55 60
Lys Asp Trp Gly Ala Lys Lys Asp Ile Lys Met Ser Pro Ala Pro Ala
65 70 75 80
Asn Lys Val Pro His Ser Ala Ala Asn Leu Pro Leu Arg Phe Gly Arg
85 90 95

Asn Ile Glu Asp Arg Arg Ser Pro Arg Ala Arg Ala Asn Met Glu Ala
100 105 110
Gly Thr Met Ser His Phe Pro Ser Leu Pro Gln Arg Phe Gly Arg Thr
115 120 125
Thr Ala Arg Arg Ile Thr Lys Thr Leu Ala Gly Leu Pro Gln Lys Ser
130 135 140
Leu His Ser Leu Ala Ser Ser Glu Ser Leu Tyr Ala Met Thr Arg Gln
145 150 155 160
His Gln Glu Ile Gln Ser Pro Gly Gln Glu Gln Pro Arg Lys Arg Val
165 170 175
Phe Thr Glu Thr Asp Asp Ala Glu Arg Lys Gln Glu Lys Ile Gly Asn
180 185 190
Leu Gln Pro Val Leu Gln Gly Ala Met Lys Leu
195 200

〈210〉 8
〈211〉 609
〈212〉 DNA

〈213〉 Rat

〈400〉 8

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tatggaaaat attaccagct gagaggaatc ccaaaagggg taaaggaaag aagtgtcact 180
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ctgccccaaa ggttttgggag aacaacagcc agacgcatca ccaagacact ggctggtttg 420
ccccagaaat ccctgcactc cctggcctcc agtgaatcgc tctatgccat gacccgccag 480
catcaagaaa ttcagagtcc tggtcaagag caacctagga aacgggtgtt cacggaaaca 540
gatgatgcag aaaggaaaca agaaaaaata ggaaacctcc agccagtcct tcaaggggct 600
atgaagctg 609

〈210〉 9

〈211〉 188

〈212〉 PRT

〈213〉 Mouse

〈400〉 9

Met Glu Ile Ile Ser Leu Lys Arg Phe Ile Leu Leu Thr Val Ala Thr
1 5 10 15
Ser Ser Phe Leu Thr Ser Asn Thr Phe Cys Thr Asp Glu Phe Met Met
20 25 30
Pro His Phe His Ser Lys Glu Gly Asp Gly Lys Tyr Ser Gln Leu Arg
35 40 45
Gly Ile Pro Lys Gly Glu Lys Glu Arg Ser Val Ser Phe Gln Glu Leu
50 55 60
Lys Asp Trp Gly Ala Lys Asn Val Ile Lys Met Ser Pro Ala Pro Ala
65 70 75 80
Asn Lys Val Pro His Ser Ala Ala Asn Leu Pro Leu Arg Phe Gly Arg

85 90 95

Thr Ile Asp Glu Lys Arg Ser Pro Ala Ala Arg Val Asn Met Glu Ala

100 105 110

Gly Thr Arg Ser His Phe Pro Ser Leu Pro Gln Arg Phe Gly Arg Thr

115 120 125

Thr Ala Arg Ser Pro Lys Thr Pro Ala Asp Leu Pro Gln Lys Pro Leu

130 135 140

His Ser Leu Gly Ser Ser Glu Leu Leu Tyr Val Met Ile Cys Gln His

145 150 155 160

Gln Glu Ile Gln Ser Pro Gly Gly Lys Arg Thr Arg Arg Gly Ala Phe

165 170 175

Val Glu Thr Asp Asp Ala Glu Arg Lys Pro Glu Lys

180 185

〈210〉 10

〈211〉 564

〈212〉 DNA

〈213〉 Mouse

〈400〉 10

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tttcaagaac taaaagattg gggggcaaag aatgttatta agatgagtcc agcccctgcc 240
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caagaaattc agagtcctgg tggaaagcga acgaggagag gagcgtttgt ggaaacagat 540
gatgcagaaa ggaaaccaga aaaa 564

〈210〉 11
〈211〉 432
〈212〉 PRT
〈213〉 Rat
〈400〉 11

Met Glu Ala Glu Pro Ser Gln Pro Pro Asn Gly Ser Trp Pro Leu Gly
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Gln Asn Gly Ser Asp Val Glu Thr Ser Met Ala Thr Ser Leu Thr Phe
20 25 30
Ser Ser Tyr Tyr Gln His Ser Ser Pro Val Ala Ala Met Phe Ile Ala
35 40 45
Ala Tyr Val Leu Ile Phe Leu Leu Cys Met Val Gly Asn Thr Leu Val
50 55 60
Cys Phe Ile Val Leu Lys Asn Arg His Met Arg Thr Val Thr Asn Met
65 70 75 80
Phe Ile Leu Asn Leu Ala Val Ser Asp Leu Leu Val Gly Ile Phe Cys
85 90 95
Met Pro Thr Thr Leu Val Asp Asn Leu Ile Thr Gly Trp Pro Phe Asp
100 105 110

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Asn Ala Thr Cys Lys Met Ser Gly Leu Val Gln Gly Met Ser Val Ser
        115                 120                 125
Ala Ser Val Phe Thr Leu Val Ala Ile Ala Val Glu Arg Phe Arg Cys
    130                 135                 140
Ile Val His Pro Phe Arg Glu Lys Leu Thr Leu Arg Lys Ala Leu Phe
145                 150                 155                 160
Thr Ile Ala Val Ile Trp Ala Leu Ala Leu Leu Ile Met Cys Pro Ser
                165                 170                 175
Ala Val Thr Leu Thr Val Thr Arg Glu Glu His His Phe Met Leu Asp
            180                 185                 190
Ala Arg Asn Arg Ser Tyr Pro Leu Tyr Ser Cys Trp Glu Ala Trp Pro
        195                 200                 205
Glu Lys Gly Met Arg Lys Val Tyr Thr Ala Val Leu Phe Ala His Ile
    210                 215                 220
Tyr Leu Val Pro Leu Ala Leu Ile Val Val Met Tyr Val Arg Ile Ala
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225 230 235 240
Arg Lys Leu Cys Gln Ala Pro Gly Pro Ala Arg Asp Thr Glu Glu Ala
245 250 255
Val Ala Glu Gly Gly Arg Thr Ser Arg Arg Arg Ala Arg Val Val His
260 265 270
Met Leu Val Met Val Ala Leu Phe Phe Thr Leu Ser Trp Leu Pro Leu
275 280 285
Trp Val Leu Leu Leu Leu Ile Asp Tyr Gly Glu Leu Ser Glu Leu Gln
290 295 300
Leu His Leu Leu Ser Val Tyr Ala Phe Pro Leu Ala His Trp Leu Ala
305 310 315 320
Phe Phe His Ser Ser Ala Asn Pro Ile Ile Tyr Gly Tyr Phe Asn Glu
325 330 335
Asn Phe Arg Arg Gly Phe Gln Ala Ala Phe Arg Ala Gln Leu Cys Trp
340 345 350
Pro Pro Trp Ala Ala His Lys Gln Ala Tyr Ser Glu Arg Pro Asn Arg
355 360 365
Leu Leu Arg Arg Arg Val Val Val Asp Val Gln Pro Ser Asp Ser Gly
370 375 380
Leu Pro Ser Glu Ser Gly Pro Ser Ser Gly Val Pro Gly Pro Gly Arg
385 390 395 400
Leu Pro Leu Arg Asn Gly Arg Val Ala His Gln Asp Gly Pro Gly Glu
405 410 415
Gly Pro Gly Cys Asn His Met Pro Leu Thr Ile Pro Ala Trp Asn Ile
420 425 430

〈210〉 12
〈211〉 1296
〈212〉 DNA
〈213〉 Rat

〈400〉 12

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ccggtggcag ccatgttcat cgcggcctac gtgctcatct tcctcctctg catggtgggc 180
aacaccctgg tctgcttcat tgtgctcaag aaccggcaca tgcgcactgt caccaacatg 240
tttatcctca acctggccgt cagcgacctg ctggtgggca tcttctgcat gcccacaacc 300
cttgtggaca accttatcac tggttggcct tttgacaacg ccacatgcaa gatgagcggc 360
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aggttccgct gcatcgtgca ccctttccgc gagaagctga ccccttcggaa ggcgctgttc 480
accatcgcgg tgatctgggc tctggcgctg ctcatcatgt gtccctcggc ggtcactctg 540
acagtcaccc gagaggagca tcacttcatg ctggatgctc gtaaccgctc ctacccgctc 600
tactcgtgct gggaggcctg gcccgagaag ggcatgcgca aggtctacac cgcggtgctc 660
ttcgcgcaca tctacctggt gccgctggcg ctcatcgtag tgatgtacgt gcgcatcgcg 720
cgcaagctat gccaggcccc cggtcctgcg cgcgacacgg aggaggcggt ggccgagggt 780
ggccgcactt cgcgccgtag ggcccgcgtg gtgcacatgc tggtcatggt ggcgctcttc 840
ttcacgttgt cctggctgcc actctgggtg ctgctgctgc tcatcgacta tggggagctg 900
agcgagctgc aactgcacct gctgtcggtc tacgccttcc ccttggcaca ctggctggcc 960
ttcttccaca gcagcgccaa ccccatcatc tacggctact tcaacgagaa cttccgccgc 1020
ggcttccagg ctgccttccg tgcacagctc tgctggcctc cctgggccgc ccacaagcaa 1080
gcctactcgg agcggcccaa ccgcctcctg cgcaggcggg tggtggtgga cgtgcaaccc 1140
agcgactccg gcctgccatc agagtctggc cccagcagcg gggtcccagg gcctggccgg 1200
ctgccactgc gcaatgggcg tgtggcccat caggatggcc cgggggaagg gccaggctgc 1260
aaccacatgc ccctcaccat cccggcctgg aacatt 1296

〈210〉 13

〈211〉 12

〈212〉 PRT

〈213〉 Artificial Sequence

〈220〉

〈223〉 the C-terminus of the polypeptide is amide (-$CONH_2$) form

〈400〉 13

Met Pro His Ser Phe Ala Asn Leu Pro Leu Arg Phe
1 5 10

〈210〉 14

〈211〉 8

〈212〉 PRT

〈213〉 Artificial Sequence

〈220〉

〈223〉 the C-terminus of the polypeptide is amide (-$CONH_2$) form

〈400〉 14

Val Pro Asn Leu Pro Gln Arg Phe
1 5

〈210〉 15

〈211〉 12

〈212〉 PRT

〈213〉 Artificial Sequence

〈220〉

〈223〉 the C-terminus of the polypeptide is amide (-$CONH_2$) form

〈400〉 15

Ser Ala Gly Ala Thr Ala Asn Leu Pro Leu Arg Ser
1 5 10

〈210〉 16

〈211〉 36

〈212〉 DNA

〈213〉 Human

〈400〉 16

atgccacact ccttcgccaa cttgccattg agattt 36

〈210〉 17

〈211〉 36

〈212〉 DNA

〈213〉 Human

〈400〉 17

agtgctggag caacagccaa cctgcctctg agatct 36

〈210〉 18

〈211〉 24

〈212〉 DNA

〈213〉 Human

〈400〉 18

gttcctaacc tgccccaaag gttt 24

〈210〉 19

〈211〉 276

〈212〉 DNA

〈213〉 Human

〈400〉 19

atggaaatta tttcatcaaa actattcatt ttattgactt tagccacttc aagcttgtta 60

acatcaaaca ttttttgtgc agatgaatta gtgatgtcca atcttcacag caaagaaaat 120

tatgacaaat attctgagcc tagaggatac ccaaaagggg aaagaagcct caattttgag 180

gaattaaaag attggggacc aaaaaatgtt attaagatga gtacacctgc agtcaataaa 240

atgccacact ccttcgccaa cttgccattg agattt 276

〈210〉 20

〈211〉 336

〈212〉 DNA

〈213〉 Human

〈400〉 20

atggaaatta tttcatcaaa actattcatt ttattgactt tagccacttc aagcttgtta 60

acatcaaaca ttttttgtgc agatgaatta gtgatgtcca atcttcacag caaagaaaat 120

tatgacaaat attctgagcc tagaggatac ccaaaagggg aaagaagcct caattttgag 180

gaattaaaag attggggacc aaaaaatgtt attaagatga gtacacctgc agtcaataaa 240

atgccacact ccttcgccaa cttgccattg agatttggga ggaacgttca agaagaaaga 300

agtgctggag caacagccaa cctgcctctg agatct 336

〈210〉 21

〈211〉 393

〈212〉 DNA

〈213〉 Human

〈400〉 21

atggaaatta tttcatcaaa actattcatt ttattgactt tagccacttc aagcttgtta 60

acatcaaaca ttttttgtgc agatgaatta gtgatgtcca atcttcacag caaagaaaat 120

tatgacaaat attctgagcc tagaggatac ccaaaagggg aaagaagcct caattttgag 180

gaattaaaag attggggacc aaaaaaatgtt attaagatga gtacacctgc agtcaataaa 240

atgccacact ccttcgccaa cttgccattg agatttggga ggaacgttca agaagaaaga 300

agtgctggag caacagccaa cctgcctctg agatctgga agaaatatgga ggtgagcctc 360

gtgagacgtg ttcctaacct gccccaaagg ttt 393

〈210〉 22

〈211〉 203

〈212〉 PRT

〈213〉 Rat

〈400〉 22

Met Glu Ile Ile Ser Ser Lys Arg Phe Ile Leu Leu Thr Leu Ala Thr
1 5 10 15

Ser Ser Phe Leu Thr Ser Asn Thr Leu Cys Ser Asp Glu Leu Met Met
20 25 30

Pro His Phe His Ser Lys Glu Gly Tyr Gly Lys Tyr Tyr Gln Leu Arg
35 40 45

Gly Ile Pro Lys Gly Val Lys Glu Arg Ser Val Thr Phe Gln Glu Leu
50 55 60
Lys Asp Trp Gly Ala Lys Lys Asp Ile Lys Met Ser Pro Ala Pro Ala
65 70 75 80
Asn Lys Val Pro His Ser Ala Ala Asn Leu Pro Leu Arg Phe Gly Arg
85 90 95
Asn Ile Glu Asp Arg Arg Ser Pro Arg Ala Arg Ala Asn Met Glu Ala
100 105 110
Gly Thr Met Ser His Phe Pro Ser Leu Pro Gln Arg Phe Gly Arg Thr
115 120 125
Thr Ala Arg Arg Ile Thr Lys Thr Leu Ala Gly Leu Pro Gln Lys Ser
130 135 140
Leu His Ser Leu Ala Ser Ser Glu Leu Leu Tyr Ala Met Thr Arg Gln
145 150 155 160
His Gln Glu Ile Gln Ser Pro Gly Gln Glu Gln Pro Arg Lys Arg Val
165 170 175
Phe Thr Glu Thr Asp Asp Ala Glu Arg Lys Gln Glu Lys Ile Gly Asn
180 185 190
Leu Gln Pro Val Leu Gln Gly Ala Met Lys Leu
195 200

〈210〉 23
〈211〉 609
〈212〉 DNA

〈213〉 Rat

〈400〉 23

atggaaatta tttcatcaaa gcgattcatt ttattgactt tagcaacttc aagcttctta 60
acttcaaaca ccctttgttc agatgaatta atgatgcccc attttcacag caaagaaggt 120
tatggaaaat attaccagct gagaggaatc ccaaaagggg taaaggaaag aagtgtcact 180
tttcaagaac tcaaagattg gggggcaaag aaagatatta agatgagtcc agcccctgcc 240
aacaaagtgc cccactcagc agccaacctt cccctgaggt ttgggaggaa catagaagac 300
agaagaagcc ccagggcacg ggccaacatg gaggcaggga ccatgagcca ttttcccagc 360
ctgccccaaa ggtttgggag aacaacagcc agacgcatca ccaagacact ggctggtttg 420
ccccagaaat ccctgcactc cctggcctcc agtgaattgc tctatgccat gacccgccag 480
catcaagaaa ttcagagtcc tggtcaagag caacctagga aacgggtgtt cacggaaaca 540
gatgatgcag aaaggaaaca agaaaaaata ggaaacctcc agccagtcct tcaaggggct 600
atgaagctg 609

〈210〉 24

〈211〉 430

〈212〉 PRT

〈213〉 Human

〈400〉 24

Met Glu Gly Glu Pro Ser Gln Pro Pro Asn Ser Ser Trp Pro Leu Ser
1 5 10 15
Gln Asn Gly Thr Asn Thr Glu Ala Thr Pro Ala Thr Asn Leu Thr Phe
20 25 30
Ser Ser Tyr Tyr Gln His Thr Ser Pro Val Ala Ala Met Phe Ile Val
35 40 45
Ala Tyr Ala Leu Ile Phe Leu Leu Cys Met Val Gly Asn Thr Leu Val
50 55 60
Cys Phe Ile Val Leu Lys Asn Arg His Met His Thr Val Thr Asn Met
65 70 75 80
Phe Ile Leu Asn Leu Ala Val Ser Asp Leu Leu Val Gly Ile Phe Cys

```
                  85                  90                  95
Met Pro Thr Thr Leu Val Asp Asn Leu Ile Thr Gly Trp Pro Phe Asp

            100                 105                 110
Asn Ala Thr Cys Lys Met Ser Gly Leu Val Gln Gly Met Ser Val Ser
        115                 120                 125
Ala Ser Val Phe Thr Leu Val Ala Ile Ala Val Glu Arg Phe Arg Cys
    130                 135                 140
Ile Val His Pro Phe Arg Glu Lys Leu Thr Leu Arg Lys Ala Leu Val
145                 150                 155                 160
Thr Ile Ala Val Ile Trp Ala Leu Ala Leu Leu Ile Met Cys Pro Ser
                165                 170                 175
Ala Val Thr Leu Thr Val Thr Arg Glu Glu His His Phe Met Val Asp
            180                 185                 190
Ala Arg Asn Arg Ser Tyr Pro Leu Tyr Ser Cys Trp Glu Ala Trp Pro
        195                 200                 205
Glu Lys Gly Met Arg Arg Val Tyr Thr Thr Val Leu Phe Ser His Ile
    210                 215                 220
Tyr Leu Ala Pro Leu Ala Leu Ile Val Val Met Tyr Ala Arg Ile Ala
```

225 230 235 240
Arg Lys Leu Cys Gln Ala Pro Gly Pro Ala Pro Gly Gly Glu Glu Ala
245 250 255
Ala Asp Pro Arg Ala Ser Arg Arg Arg Ala Arg Val Val His Met Leu
260 265 270
Val Met Val Ala Leu Phe Phe Thr Leu Ser Trp Leu Pro Leu Trp Ala
275 280 285
Leu Leu Leu Leu Ile Asp Tyr Gly Gln Leu Ser Ala Pro Gln Leu His
290 295 300
Leu Val Thr Val Tyr Ala Phe Pro Phe Ala His Trp Leu Ala Phe Phe
305 310 315 320
Asn Ser Ser Ala Asn Pro Ile Ile Tyr Gly Tyr Phe Asn Glu Asn Phe
325 330 335
Arg Arg Gly Phe Gln Ala Ala Phe Arg Ala Arg Leu Cys Pro Arg Pro
340 345 350
Ser Gly Ser His Lys Glu Ala Tyr Ser Glu Arg Pro Gly Gly Leu Leu
355 360 365
His Arg Arg Val Phe Val Val Val Arg Pro Ser Asp Ser Gly Leu Pro
370 375 380
Ser Glu Ser Gly Pro Ser Ser Gly Ala Pro Arg Pro Gly Arg Leu Pro
385 390 395 400
Leu Arg Asn Gly Arg Val Ala His His Gly Leu Pro Arg Glu Gly Pro
405 410 415
Gly Cys Ser His Leu Pro Leu Thr Ile Pro Ala Trp Asp Ile
420 425 430

〈210〉 25
〈211〉 1290
〈212〉 DNA
〈213〉 Human

〈400〉 25

atggaggggg agccctccca gcctcccaac agcagttggc ccctaagtca gaatgggact 60
aacactgagg ccaccccggc tacaaacctc accttctcct cctactatca gcacacctcc 120
cctgtggcgg ccatgttcat tgtggcctat gcgctcatct tcctgctctg catggtgggc 180
aacaccctgg tctgtttcat cgtgctcaag aaccggcaca tgcatactgt caccaacatg 240
ttcatcctca acctggctgt cagtgacctg ctggtgggca tcttctgcat gcccaccacc 300
cttgtggaca acctcatcac tgggtggccc ttcgacaatg ccacatgcaa gatgagcggc 360
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aggttccgct gcatcgtgca ccctttccgc gagaagctga ccctgcggaa ggcgctcgtc 480
accatcgccg tcatctgggc cctggcgctg ctcatcatgt gtccctcggc cgtcacgctg 540
accgtcaccc gtgaggagca ccacttcatg gtggacgccc gcaaccgctc ctaccctctc 600
tactcctgct gggaggcctg gcccgagaag ggcatgcgca gggtctacac cactgtgctc 660
ttctcgcaca tctacctggc gccgctggcg ctcatcgtgg tcatgtacgc ccgcatcgcg 720
cgcaagctct gccaggcccc gggcccggcc ccccgggggcg aggaggctgc ggacccgcga 780
gcatcgcggc gcagagcgcg cgtggtgcac atgctggtca tggtggcgct gttcttcacg 840
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ccgcagctgc acctggtcac cgtctacgcc ttccccttcg cgcactggct ggccttcttc 960
aacagcagcg ccaaccccat catctacggc tacttcaacg agaacttccg ccgcggcttc 1020
caggccgcct tccgcgcccg cctctgcccg cgcccgtcgg ggagccacaa ggaggcctac 1080
tccgagcggc ccggcgggct tctgcacagg cgggtcttcg tggtggtgcg gcccagcgac 1140
tccgggctgc cctctgagtc gggccctagc agtggggccc ccaggcccgg ccgcctcccg 1200
ctgcggaatg ggcgggtggc tcaccacggc ttgcccaggg aagggcctgg ctgctcccac 1260
ctgcccctca ccattccagc ctgggatatc 1290

〈210〉 26
〈211〉 1290
〈212〉 DNA
〈213〉 Human
〈400〉 26

atggaggggg agccctccca gcctcccaac agcagttggc ccctaagtca gaatgggact 60

aacactgagg ccacccggc tacaaacctc accttctcct cctactatca gcacacctcc 120

cctgtggcgg ccatgttcat tgtggcctat gcgctcatct tcctgctctg catggtgggc 180
aacaccctgg tctgtttcat cgtgctcaag aaccggcaca tgcatactgt caccaacatg 240
ttcatcctca acctggctgt cagtgacctg ctggtgggca tcttctgcat gcccaccacc 300
cttgtggaca acctcatcac tgggtggccc ttcgacaatg ccacatgcaa gatgagcggc 360
ttggtgcagg gcatgtctgt gtcggcttcc gttttcacac tggtggccat tgctgtggaa 420
aggttccgct gcatcgtgca ccctttccgc gagaagctga ccctgcggaa ggcgctcgtc 480
accatcgccg tcatctgggc cctggcgctg ctcatcatgt gtccctcggc cgtcacgctg 540
accgtcaccc gtgaggagca ccacttcatg gtggacgccc gcaaccgctc ctacccgctc 600
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cgcaagctct gccaggcccc gggcccggcc cccgggggcg aggaggctgc ggacccgcga 780
gcatcgcggc gcagagcgcg cgtggtgcac atgctggtca tggtggcgct gttcttcacg 840
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ctgcggaatg ggcgggtggc tcaccacggc ttgcccaggg aagggcctgg ctgctcccac 1260
ctgcccctca ccattccagc ctgggatatc 1290

〈210〉 27
〈211〉 430
〈212〉 PRT
〈213〉 Mouse
〈220〉
〈400〉 27

Gly Glu Pro Ser Gln Pro Pro Asn Gly Ser Trp Pro Pro Ser Leu Arg
5 10 15
Glu Ser Asp Ala Glu Thr Ala Pro Val Ala Ser Leu Thr Phe Ser Ser

```
                20                  25                  30
Tyr Tyr Gln His Ser Ser Pro Val Ala Ala Met Phe Ile Ala Ala Tyr
            35                  40                  45
Ala Leu Ile Phe Leu Leu Cys Met Val Gly Asn Thr Leu Val Cys Phe
        50                  55                  60
Ile Val Leu Lys Asn Arg His Met Arg Thr Val Thr Asn Met Phe Ile
65                  70                  75                  80
Leu Asn Leu Ala Val Ser Asp Leu Leu Val Gly Ile Phe Cys Met Pro
                85                  90                  95
Thr Thr Leu Val Asp Asn Leu Ile Thr Gly Trp Pro Phe Asp Asn Ala
            100                 105                 110
Thr Cys Lys Met Ser Gly Leu Val Glu Gly Met Ser Val Ser Ala Ser
        115                 120                 125
Val Phe Thr Leu Val Ala Ile Ala Val Glu Arg Phe Arg Cys Ile Val
    130                 135                 140
His Pro Phe Arg Glu Lys Leu Thr Leu Arg Lys Ala Leu Leu Thr Ile
145                 150                 155                 160
Ala Val Ile Trp Ala Leu Ala Leu Leu Ile Met Cys Pro Ser Ala Val
                165                 170                 175
Thr Leu Thr Val Thr Arg Glu Glu His His Phe Met Leu Asp Ala Arg
            180                 185                 190

Asn Arg Ser Tyr Pro Leu Tyr Ser Cys Trp Glu Ala Trp Pro Glu Lys
        195                 200                 205
Gly Met Arg Lys Val Tyr Thr Ala Val Leu Phe Ala His Ile Tyr Leu
    210                 215                 220
Ala Pro Leu Ala Leu Ile Val Val Met Tyr Ala Arg Ile Ala Arg Lys
```

225 230 235 240
Leu Cys Gln Ala Pro Gly Pro Ala Arg Asp Ala Glu Glu Ala Val Ala
245 250 255
Glu Gly Gly Arg Ala Ser Arg Arg Arg Ala Arg Val Val His Met Leu
260 265 270
Val Met Val Ala Leu Phe Phe Thr Leu Ser Trp Leu Pro Leu Trp Val
275 280 285
Leu Leu Leu Leu Ile Asp Tyr Gly Glu Leu Ser Glu Leu Gln Leu His
290 295 300
Leu Leu Ser Val Tyr Ala Phe Pro Leu Ala His Trp Leu Ala Phe Phe
305 310 315 320
His Ser Ser Ala Asn Pro Ile Ile Tyr Gly Tyr Phe Asn Glu Asn Phe
325 330 335
Arg Arg Gly Phe Gln Ala Ala Phe Arg Ala Gln Leu Cys Trp Leu Pro
340 345 350
Trp Ala Ala His Lys Gln Ala Tyr Ser Glu Arg Pro Gly Arg Leu Leu
355 360 365
Arg Arg Arg Val Val Val Asp Val Gln Pro Ser Asp Ser Gly Leu Pro
370 375 380
Ser Glu Ser Gly Pro Ser Ser Gly Val Pro Gly Pro Asn Arg Leu Pro
385 390 395 400
Leu Arg Asn Gly Arg Val Ala His Gln Asp Gly Pro Arg Glu Gly Pro
405 410 415
Gly Cys Asn His Met Pro Leu Thr Ile Pro Ala Trp Asn Ile
420 425 430

〈210〉 28
〈211〉 16984
〈212〉 DNA
〈213〉 Mouse

〈220〉

〈221〉 CDS

〈222〉 (4706)..(5021)

〈220〉

〈221〉 CDS

〈222〉 (14061)..(14160)

〈220〉

〈221〉 CDS

〈222〉 (15476)..(16349)

〈400〉 28

caagttgccg ggcttgggag gtggggaaga gacaggggag tggcagtgag tgaggtggga 60
gggagtgggt tttctttatt taaacgtgca cttgtgtgtg tgtgtgtgtg tgtgtgtgtg 120
tgtgtgtgat gtatatgtgt gtggagacgt gattaggata tgagtgaaga tcagagggca 180
gtctgtgtgt gggagtgggg tctctcctcc taccacgtag gtcccaggga tcaaactcgg 240
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accttaaacc tctcatcctt ctgcctctgg agttctaggg gtatgggtgt accctagccc 420
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ctatttaaaa aaaaaaagat gcaaaactat ttttcagtga aaaggaatgt cggctgacac 600
tcgcttcaga gcaactgagg aggaaagtca atggatgctg caggtggaca gacttcccgt 660
gggagtcctt tttaccattc catttctcat ggttcattaa actttatact tctgcatgtg 720
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gtgtttgaat gctgttggag ctcttgaaag gcctgtgtgt gggggagtac catcatctct 840
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cagcaggggg tgcaaagaga aagaataggt tgctatggtt gcttgggagt tctagaagca 1920
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cacacacaca cacacacaca tacacaccac acacacacac acacaccaca gagagagaga 3000
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tatcacatac agtgtacagg ttgacacact tcatctcagc actcaggtgg tagaggcagg 3600
agggtaagag ttcagggcca tccttagcta aagtggtgag ttcaaggcca gcctgatatg 3660
gaagaccttg tcacccaaga agtcttctga gacccaaaag atgacatgaa gcacagggag 3720
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〈213〉 Mouse

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[Brief Description of the Drawings]
[Drawing 1] The schematic diagram of OT7T022 targeting vector is shown.

[Translation done.]

DESCRIPTION OF DRAWINGS

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[Drawing 1] The schematic diagram of OT7T022 targeting vector is shown.

[Translation done.]